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VOL. 1, 1922

THE JOURNAL

OF

METABOLIC RESEARCH

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Published Monthly by
THE PHYSIATRIC INSTITUTE
Morristown, New Jersey, U. S. A.
PRICE: \$10.00 PER YEAR

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INTRODUCTORY REMARKS.

THE writer has tried for the past year to obtain publication of the series of papers on diabetic pathology, which begins in this issue. It was rejected by some journals, and accepted by a larger number on the condition of a formidable subsidy. In most instances also the proposed plan of publication was slow, so that the unity of the series would have been spoiled and the final paper might not have appeared for another year. Similar difficulties known to have been encountered by other metabolic workers emphasized the need of a medium which would publish such investigations promptly and fully, and the important service which a journal of this character could render to the subject of metabolism.

Letters were therefore addressed to leading investigators, proposing the establishment of a Journal of Metabolic Research. Five answers, some of them from persons of the highest authority, were adverse, on the ground that existing journals were sufficient and the number should not be increased, or that other journals were to be launched which would cover this field. A larger number of the correspondents endorsed the project but excused themselves from participation for personal reasons. The overwhelming majority, however, pledged themselves heartily to the undertaking from the outset, and the unexpectedly strong support thus received was responsible for carrying forward the plans more rapidly than originally contemplated.

Though metabolism is essentially a division of physiology or chemistry, dealing with nutritive, internal secretory and related functions, its intelligent study demands additional information gathered from morphology, general biology, pathology, and several departments of medicine. It is believed that the representation of workers in these different branches on the editorial staff gives assurance of adequate scope and variety of contributed articles and trustworthy judgment on questions arising in the various ramifications of the subject. The collaboration of a staff of this character is the basis of

hope that this Journal will succeed in its purpose of expressing and assisting the development of this scientific field.

The Journal is intended to serve for publication of the results of original research. As it occupies a border zone between the laboratory and the clinic, it should be of interest to laboratory and clinical investigators and to such medical practitioners as wish to keep in touch with fundamental scientific progress in metabolism. Reviews or other non-experimental articles will ordinarily not be published. The subject of metabolism, however, is in such a state that occasional exceptions may be made in favor of reviews which summarize new investigations or clarify a confused topic in such a manner as to assist research and entitle them to rank as distinct contributions. For the same reason, no arbitrary limit will be placed on the length of papers. Editorial difficulties will thus be increased, in enforcing all possible brevity and eliminating literary references which are so familiar or easily accessible as to be unnecessary. Nevertheless, consideration of the literature is often important for the logical presentation of the material in hand, and the most thorough experimental work is that which may suffer most by irrational limitation of space. Papers of one page and of one hundred pages may be equally appropriate, provided they express significant facts in the briefest form compatible with completeness.

A few words may be devoted to the style of literary citations adopted. Scarcely any libraries now number the bound copies of their journals with Roman numerals, for the reason that the average reader must pause for an instant or two to figure out what these mean. Likewise, most persons who have to consult much literature realize the waste of time and attention occasioned by the Roman numbered references, and also the fact that these are probably responsible for more errors of citation than any other one cause. For these reasons there seems to be a tendency for the newer reference periodicals to drop the older designation of volumes in the Roman form and substitute some clear arrangement of Arabic numbers. Accordingly, it is requested that in this Journal references be composed of, first, the standard abbreviation of the name of the journal cited, second the Arabic number of the volume, third the year, and fourth the page. The title of the paper

quoted may follow or may be omitted, according to the author's preference. Examples will be found in the present issue.

The attempt will be made to publish manuscripts promptly, within a month or two after their receipt. Authors will receive one hundred free reprints of each paper; larger numbers must be ordered in advance at a set price. The nature of metabolic investigations frequently imposes heavy expenses for tables, illustrations and the like. An important service of a journal in this field will be to lift this burden as far as possible from investigators and their laboratory funds. Obviously, writers must be asked to be reasonable, and to refrain from expressing in an expensive form that which could be equally clearly conveyed in some less costly manner. When the expense is exceptionally high, more or less assistance may be required. Decisions of this kind may fairly be influenced not only by the financial ability of this Journal but also by that of the institution from which the research is published. The deficit to be expected in publishing a journal on these lines practically represents an endowment of this branch of study to this extent.

The editor must assume the burden and responsibility of the routine management. Doubtful questions of general or detailed character will be settled with the advice of the editorial staff as a whole or of those members who may be specially qualified to judge the points at issue. Such advice, for example, on the acceptance or rejection of manuscripts may obviate charges of personal bias, and will make the scientific standard and policy of the Journal representative of the character of the editorial board. As far as suitable papers from other sources may be lacking for the early numbers of the Journal, the space will be occupied by publications of the writer and associates; but it is not intended that the work of others shall thus be crowded out or that the Physiatrie Institute shall hold either monopoly or priority. The purpose in view is helpfulness to students of metabolism, and contributions are solicited from all workers in the subject both in this country and abroad.

FREDERICK M. ALLEN

EXPERIMENTAL STUDIES IN DIABETES.

SERIES III. THE PATHOLOGY OF DIABETES *

I. HYDROPIC DEGENERATION OF ISLANDS OF LANGERHANS AFTER PARTIAL PANCREATECTOMY.

BY FREDERICK M. ALLEN

*From the Hospital of the Rockefeller Institute for Medical Research,
New York.*

As knowledge of the etiology and pathology is highly important for both the theoretical understanding and the therapeutic control of any morbid condition, the writer's first research, published in 1913¹, included a study of the pancreatic changes in experimental diabetes. The continuation of this investigation, as detailed in the following series of papers, has developed a general theory of diabetic pathology, which was outlined in a preliminary publication in 1919².

The present paper deals with the so-called hydropic degeneration of the islands of Langerhans. This change was first observed and clearly described in human cases by Weichselbaum and Stangl³, who ranked it on a par with other forms of degeneration. The research above mentioned¹ first demonstrated this change in experimental animals and established it as a specific diabetic phenomenon, representing the exhaustion and breakdown of cells by over-stimulation of an internal secretory function due to feeding in excess of the weakened assimilative power. Homans⁴ proved that the process is limited to the beta cells in experimental and human diabetes. Reference may be made to these various publications for a general description and discussion.

The present investigation gives some details of the conditions under which this degeneration occurs and some additional features of the picture in experimental animals. Obser-

* No separate reprints will be made of these papers, but on completion of the series they will be bound together in the form of a monograph.

vations will first be reported concerning (1) the time of development of hydropic degeneration, (2) its reversibility, (3) its relation to diabetic symptoms, (4) its diagnostic and prognostic status, (5) the character of the change.

(1) TIME OF DEVELOPMENT.—This can obviously not be uniform, as it is governed by the severity of the diabetes, which in turn is dependent upon the size of the pancreas remnant and the diet. Some influence also is evidently exerted by inflammation, and small remnants are naturally more subject to trauma than large ones. In a general way the experience summarized in the tables defines the time limits of hydropic degeneration as follows:

(a) *Beginning*.—In the first experiments in Table 2, very small pancreas remnants were left, so as to produce a quick onset of severe diabetes. There is early and marked hyperglycemia in such cases, though glycosuria is always delayed longer than after total pancreatectomy. The early inflammatory changes are chiefly interlobular, and even when the lobules are invaded the central position of the islands generally affords them some protection in comparison with the acinar tissue. Inflammation, however, in addition to the intensity of the diabetes, may have contributed to the apparent disappearance of beta cells within 8 days in dog No. 7, with the exceptionally small remnant of only 1/70 of the pancreas. Otherwise, the beginning of definite vacuolation in the island cells seemed to require about 5 days, and only the incipient degrees were present at the end of a week. Confirmatory observations are found in Table 3. For example, dog No. 2, possessing only 1/21 of the pancreas, showed only the slightest hydropic appearances in 4 days. Dog No. 1, with milder diabetes, showed no vacuolation in 3 days and also none for 7 days following a second operation.

(b) *Duration*.—The progress of hydropic degeneration varies with the intensity of the diabetes, but Table 2 shows that with average conditions of unchecked diabetes the maximal vacuolation may be expected in about 1 month. Dog No. 16 thus showed submaximal vacuolation of nearly all beta cells in the pancreas. In Table 3, the remnant of 1/20 in dog No. 12 was smaller than is usually chosen for long experiments. Accordingly, there was advanced vacuolation of the majority of cells of all islands in 3 weeks, but there was

no noticeable further change during the next 5 days. Dog No. 13, with milder diabetes, showed a moderate grade of hydropic change in 3 weeks, and the maximal stage was then reached 2 weeks after the second operation. The average duration of the stage of extreme vacuolation may be reckoned as about a week. During this time the hydropically swollen cells are rapidly degenerating and being lost, while the acinar tissue apparently fills in the spaces thus left. Accordingly, from this point onward the number and size of islands diminish. Approximately 5 or 6 weeks may be the time required for severe unchecked diabetes to reduce all islands to small clumps of normal appearing alpha cells and a few extremely degenerated beta cells. After 6 weeks to 2 months all beta cells may have disappeared, and the little groups of alpha cells may be difficult to recognize except with the special granule stains. These time limits vary with the severity of the diabetes. Examples are to be found in Tables 2 and 3.

(2) REVERSIBILITY. — As indicated by several observations in the tables, the pancreas may remain in the stage of full-blown hydropic change, with almost all cells of all islands clear and swollen to the maximal degree, for at least 5 days. The individual cells must therefore be able to survive in this condition during this period of the most intense diabetes. It is not certain whether the nuclear changes or the bursting of the cell membrane determine the death of the cell. The question arises up to what point the cell retains the power of recovery, and at what point the process becomes irreversible. Numerous experiments on this question were performed on both dogs and cats, according to the following plan. Diabetes is first produced by the usual operation, followed by a diet which maintains continuous heavy glycosuria. At a time when it is estimated that the majority of island cells are fully vacuolated, a second operation is performed, removing the smallest possible bit of pancreas for microscopic examination. Fasting is then used in the attempt to stop glycosuria, and after a period of freedom from symptoms on low diet additional tissue is removed for comparison. If it were possible to demonstrate marked vacuolation of most island cells before the fasting treatment, and equally large and numerous islands filled with normal cells after the treatment, this would demonstrate a restoration of the vacuolated

cells. A seeming alternative, namely that the vacuolated cells might be replaced by new healthy cells, is contrary to fact, because when the islands become reduced in size through hydropic degeneration they remain small forever after, as proved by the small islands found in many animal and human autopsies after months and years of controlled diabetes. The details of these experiments may be omitted in the interest of brevity. The proper stage of vacuolation is not always correctly guessed for the second operation. The experiments showed that a decisive demonstration as outlined is impossible. If pancreatic tissue is removed at the desired stage of maximal vacuolation, either the diabetes is already hopeless or the slight trauma of the operation makes it so, for it is impossible to stop the glycosuria thereafter, and with continued symptoms rapid destruction of islands occurs as above mentioned. Two less satisfactory methods are left. One is to perform the second operation at an earlier stage of vacuolation; the diabetes can then be checked, but the differences between islands in neighboring portions of the pancreas, as respects both normal size and structure and the rate of hydropic change, hinder judgment concerning the point at which cells lose the power of recovery. The other method is to omit the second operation, and judge the degree of probable hydropic change by control animals; but uncertainty is introduced by the variations among such animals even under identical conditions. Some conclusions can be drawn from the accumulated results of experience, as follows.

First, when the functional over-stimulation is relieved, cells in the earlier stages of vacuolation apparently can recover their normal form and granulation. This is indicated by the facts that the microscopic pictures suggest no fatal degree of injury, the animals are able to recover a considerable carbohydrate tolerance, and the pancreas remnant may subsequently be found to contain the full normal number and size of islands.

Second, the majority of cells in the stage of extreme vacuolation ordinarily degenerate and are lost. This is evidenced by the nuclear and other degenerative changes microscopically, and by the fact that animals saved by diet treatment after reaching the stage of marked vacuolation show a perma-

nent reduction of tolerance and reduction of island tissue thereafter.

Third, it is probable that some cells recover even after being widely swollen and vacuolated. The exact point beyond which recovery is impossible has not been learned, for the reasons stated. But even after the cell body is a large clear vesicle, the nucleus for a time appears thoroughly normal, so that a restoration of the cytoplasm is not improbable. Also, from 1 to 2 weeks after the control of diabetes by diet a few island cells are sometimes found which are large and partly clear, partly granulated. As it is improbable that vacuolation is progressing at this stage, the inference is that it is receding and that these are cells which have been swollen and clear and are regaining normal size and granulation.

3. RELATION TO DIABETIC SYMPTOMS.—Active diabetes is prerequisite for the occurrence of hydropic degeneration, and the two are parallel in degree and course. Table 1 shows that when diabetes fails to develop there is also no hydropic degeneration, within a time up to 2 years after operation. Table 2 shows the parallelism of diabetic symptoms and island changes in both time and severity. When the diabetes progresses rapidly, the island degeneration corresponds. When, as in experiments 30 to 34, the diabetes is kept under control for many months and then allowed to develop in mild or severe form, the island changes are of a grade corresponding to the period of symptoms and not to the total period since operation. The same point is illustrated by the repeated operations in Table 3. When diabetes is absent or too slight, vacuolation is absent. When diabetes is brought on either by removal of more tissue or by diet, vacuolation is found accordingly. Table 4 shows that partial pancreatectomy to the extent sufficient for severe diabetes is followed by no hydropic degeneration when the diabetes is thoroughly controlled by diet. The hydropic change never occurs in any condition other than diabetes, as proved by many observations to be reported in subsequent papers.

An idea of the function of the beta cells can also be deduced from the condition of the animals in which they have been completely lost. The D:N ratio of such dogs is approximately 2.8, the same as occurs in totally depancreatized dogs, unless

sometimes lowered by cachexia. The diabetes is entirely hopeless, like that following total pancreatectomy, and the animals are generally emaciated. In other respects there is a decided difference from totally depancreatized dogs. The asthenia is generally much less. Wounds ordinarily heal almost as in normal dogs, in contrast to totally depancreatized dogs in which pus may burrow through the successive suture layers of an abdominal wound to cause death from peritonitis. The duration of life is also longer, apart from complications. By special care with high fat diets, such a dog possessing adequate digestive power may retain a sleek and well nourished appearance and die in coma without emaciation (dog B2-80, Fig. 7 of paper 5 of series 1⁵; also Fig. 13 of the present paper). Particularly human cases show that the most extreme acidosis may occur with no extensive loss of beta cells. Furthermore, fatal acidosis in non-diabetic fasting puppies or fasting phlorizinized dogs produces no vacuolation of islands. A specific relation between these cells and acidosis is thus excluded, and the same is true of lipemia. The conclusion therefore seems justified that the beta cells are the sole producers of the internal secretion which is essential for carbohydrate metabolism; and when they are exhausted or lost the animal is as completely unable to use carbohydrate as a totally depancreatized animal, notwithstanding the presence of large masses of acinar, centroacinar, duct and alpha cells. The differences which still exist between such an animal and a totally depancreatized animal apparently indicate, first, that the profound cachexia of the totally depancreatized animal is not due solely to the lack of carbohydrate utilization or the glycosuria, hyperglycemia or any other consequence of this; second, that some other cells in the pancreas must furnish an unknown secretion which is not directly concerned in sugar metabolism but is somehow important for the welfare of the organism.

4. DIAGNOSTIC AND PROGNOSTIC STATUS.—As the hydropic change represents the exhaustion and degeneration of cells by functional over-stimulation, it is diagnostic of active diabetes. It may occur with hyperglycemia without glycosuria (dog No. 3, Table 3). Its absence obviously does not exclude diabetes, as it is absent when diabetic symptoms are prevented by diet or cachexia. The prognosis is bad in proportion

as the islands are found degenerated, with due allowance for the various relations discussed above. A question of some interest is presented by a group of border line cases, in which hyperglycemia and glycosuria are present for a longer or shorter period after partial pancreatectomy and then cease. When the symptoms are brief and slight, no vacuolation is found; but with intensive starch and sugar feeding heavy glycosuria may be kept up for 2 weeks or more, and slight but distinct hydropic changes may be found at this time. It is evident that the condition is a true temporary diabetes. The island cells, though worked beyond their normal limit, manage to maintain their function until the digestion fails or until subsidence of inflammation or hypertrophy of the remnant brings a genuine termination of the diabetes. With this relief of over-function the hydropic changes in the islands disappear.

5. THE CHARACTER OF THE HYDROPIK CHANGE. — As clinical studies do not reveal the true nature of the hydropic alteration, this was wrongly classified by Weichselbaum. It bears no microscopic resemblance to hyalin, colloid or amyloid degeneration. Cells in various parts of the body may undergo a form of disintegration in which their cytoplasm becomes pale and seems to dissolve, but this is sharply distinguishable from the specific process in the Langerhans islands. In the latter, the nucleus appears thoroughly normal at first; the cell membrane is clearly defined; and in particular the vacuoles have a characteristic bright appearance which most nearly resembles the Armanni vacuolation of renal cells or fat vacuoles in the liver. As the latter phenomena are found also in diabetes, a differentiation is necessary between them and the pancreatic process. The Armanni change was also first described as a degeneration, and was referred to as "vitreous degeneration" by some writers on account of the bright appearance of the vacuoles. It has since often been known as glycogenic degeneration or infiltration, because of Ehrlich's demonstration of glycogen in the vacuoles. Such glycogen deposits in a definite segment of the renal tubules occur in all prolonged glycosurias, whether or not there is hyperglycemia; for example, they may be found in phlorizin glycosuria. The writer also observed one marked instance in a diabetic dog with prolonged hyperglycemia and absence

of glycosuria on account of so-called renal impermeability. It is wrong to attribute the vacuolation invariably to glycogen, for with lipemia the same cells show a similar vacuolation from fat, and in diabetic lipemia Sudan stains may show the vacuole to be filled chiefly with fat, while stains with Best's carmine show glycogen granules distributed around the periphery of the vacuoles. The process in the kidney seems to consist merely in certain cells stuffing themselves with materials obtained either from the blood or from the filtrate in the tubules. A three-fold distinction can be drawn between the pancreatic changes and those in either the kidney or the liver. First, the former are strictly specific to diabetes while the latter are not. Second, the vacuoles in the pancreatic islands never contain either fat or glycogen. The absence of lipoids is easily demonstrated by both osmic and Sudan stains, and the absence of glycogen has been proved in some beautiful preparations with Best's carmine in which leukocytes in the capillaries are seen crammed with red granules while the swollen island cells are completely empty. Third, the filling of kidney or liver cells with glycogen or fat apparently never leads to their destruction unless some other cause of injury is present, while the vacuolation of Langerhans cells is part of a process which if continued destroys them.

At the same time, the hydropic change in the islands is distinguished from the hyalin and other degenerations mentioned, not only by the microscopic appearances but especially by the fact that it is not primarily degenerative in nature. It is not in its beginning an expression of any injury or impairment of vitality of the cells affected, but is purely a functional exhaustion, comparable to the emptying of the acinar cells of the pancreas under the stimulus of secretin or of the chromaffin cells of the adrenal medulla under certain stimuli. A distinction here is that in the case of the Langerhans cells the exhaustion is carried to the point of anatomic destruction of the cells. Whether or not future studies may furnish parallels elsewhere in the body, at present this process in the pancreatic islands is a strictly unique example of anatomic breakdown of cells under an internal secretory stimulus.

TABLE 1.

Pancreas Operations not Producing Diabetes

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
1	8.9	20 days	Bread diet, no glycosuria.	normal
2	4.5	3 weeks	Bread diet with glucose up to 300 gm. daily. Heavy exercise on treadmill. No glycosuria.	normal
3	5.6	1 month	Bread and glucose. No glycosuria.	normal
4	5.6	2½ mos.	Bread and glucose. No glycosuria.	normal
5	Body and splenic process.	3 months	Bread diet, glucose 200 gm. additional on last 2 days. No glycosuria.	normal
6	5.6	3 months	Bread diet. No glycosuria.	normal
7	Splenic process and most of body	1 month	Bread diet. No glycosuria.	normal
	Uncinate process	1 month	Bread and glucose diet. No glycosuria.	normal
	4 gm. additional.	1 month	Bread and 200 gm. glucose daily. No glycosuria.	normal
	1 gm. additional.	5 days	Bread diet. No glycosuria.	normal
8	8.9	1 month	Bread diet. Glycosuria present one week, absent thereafter.	normal
	0.5 gm. additional	2 weeks	Bread diet. No glycosuria.	normal

TABLE 1.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
	0.5 gm. additional	2 months	Glycosuria on bread diet at first, disappearing as anorexia and cachexia developed.	normal
9	Uncinate process (over 1/3 of pancreas).	3 weeks	Bread. No glycosuria.	normal
	Splenic process (1/3 of pancreas).	2 years	Mixed or meat diet. Numerous short periods of glycosuria, with long intervening periods of sugar-freedom. Glycosuria for a few days before death.	Remnant nearly 1/3 pancreas. Considerable diffuse fibrosis. Islands scarce and small, often apparently replaced by scar tissue. No vacuolation.
10	Splenic process	2½ mos.	Bread diet, with occasional glucose tests.	Normal. No vacuolation.
	Most of body of pancreas.	3¼ mos.	Bread diet, with occasional glucose tests.	normal

TABLE 2.
Diabetes After Single Operations

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
1	19/20	5 hours	Fasting. No glycosuria.	Marginal and interlobular masses of fibrin, red and white corpuscles. Acinar cells swollen and blurred, staining often atypically, nuclei indistinct. Islands intact; no vacuolation.
2	12/13	18 hours	Fasting. No glycosuria.	Marked edema of interlobular septa. No change inside lobules. Vacuolation of islands doubtful.
3	34/35	1 day	Fasting. No glycosuria. Plasma sugar 0.232%.	Edema and leukocytic infiltration of interlobular connective tissue, with frequent hemorrhages. Slight interlobular infiltration. Degeneration of acini in patches. Islands protected by internal position. No vacuolation.
4	16/17	2 days	Fasting. No glycosuria.	Markedly edematous interlobular septa. No changes inside lobules. Doubtful vacuolation of a few island cells.
5	13/14	3 days	Fasting. No glycosuria.	Hemorrhagic infiltration of interlobular septa. Pale stain of acini; much invol-

TABLE 2.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
6	9/10	5 days	Bread. Poor appetite.	<p>ution. Atypical appearance of pallor in some island cells, perhaps inflammatory edema.</p> <p>Slight vacuolation in small minority of island cells.</p>
7	69/70	5 days	Fasting, with glycosuria.	<p>Fibrosis invading margins of tiny remnant. Acinar cells swollen and markings blurred. A few tiny groups, probably of A cells, seem to be the only remains of islands.</p>
8	12/13	1 week	Bread.	<p>Remnant grossly inflamed; weight increased from 2 gm. to 5.9 gm. Interlobular septa swollen, infiltrated with red and white corpuscles. Parenchyma frequently invaded by round cells and leukocytes. Acini swollen and dimly staining; sometimes involuted. Probable proliferation of ducts. Islands few and small, containing a few vacuolated cells.</p>
9	12/13	7 days	Fasting, with glycosuria.	<p>Incipient vacuolation in minority of island cells.</p>

TABLE 2.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
10	7/8	7 days	Bread 4 days.	Incipient vacuolation in some island cells.
11	12/13	7 days	Bread.	Fully developed fibrosis in some slides. Others normal except for hydrops of about one third of all cells, varying in degree from incipient to maximal vacuolation.
12	10/11	8 days	Bread and meat.	Active inflammation with marked intra-lobular fibrosis in most slides, none in others. Much destruction of islands. Slight vacuolation.
13	12/13	8 days	Bread.	Marked vacuolation in a few island cells.
14	28/29	11 days	Suet	Diffuse pancreatitis. Most acini normal; involution in a few. Islands not invaded; marked vacuolation in minority of cells.
15	8/9	3 weeks	Meat 2 weeks. Fasting with glycosuria 1 week.	Remnant hypertrophied from 4.7 gm. to 7.6 gm. Normal in gross. No fibrosis. Acini often small. Islands scarce, small; vacuolation of half or less of their cells;

TABLE 2.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
16	8.9	3 weeks	Heavy glycosuria on bread diet, 2 weeks later on protein-fat.	vacuolation also in small ducts. Various stages of vacuolation of great majority of cells of all islands.
17	5.6	1 month	Glycosuria first 2 weeks on bread and glucose, then glycosuria and acidosis on protein-fat.	Islands numerous, large, majority of cells widely swollen and vacuolated.
18	7.8	5 weeks	Glycosuria and acidosis on mixed diet.	Islands absent except small groups interpreted as A cells, and rare, widely vacuolated B cells. Universal vacuolation of small ducts and cell-cords and cell-heaps formed from them. Normal ganglia.
19	15.16	7 weeks	Fasting and fat feeding. Very little protein. Slight continuous glycosuria.	Islands vary from complete vacuolation of all cells to absence of any vacuolation; also occasional small remains probably composed of A cells.
20	16.17	2 months	Undernutrition protein-fat diets pushed too close to verge of tolerance, so that traces of glycosuria were frequent.	Slight vacuolation of some islands.

TABLE 2.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
21	5.6	2 months	Continuous glycosuria, first on bread, then on meat diet.	Some islands large, with almost all cells maximally vacuolated. Others are small barely recognizable remains, in which granulated A cells and exhausted B cells are demonstrable by special stains.
22	4.5	2½ mos.	Glycosuria, acidosis and lipema.	Slight diffuse fibrosis. Acini slightly distorted but well filled, with little involution. Islands slightly reduced in number; maximal vacuolation of a majority of cells. No vacuolation of ducts.
23	8.9	11 weeks	Protein-fat diet 2 months, without glycosuria. Thereafter glycosuria and acidosis on mixed diet 3 weeks.	Islands reduced to small groups of normal appearing (apparently A) cells and maximally vacuolated B cells. Some small ducts and cell-cords also vacuolated.
24	8.9	3 months	Bread with heavy glycosuria 5 weeks. Fasting 25 days, low protein-fat diet 26 days. Continuous hyperglycemia; occasional traces of glycosuria.	Tissue presents almost unbroken expanses of acini. Islands almost absent; the only remains are rare small areas of normal appearing (presumably A) cells, and maximally vacuolated B cells.

TABLE 2.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
25	6 7	3 $\frac{3}{4}$ mos.	Protein-fat diet, with glycosuria and acidosis, mild at first, heavy during last 2 weeks.	Islands in some areas maximally vacuolated, in others vacuolation not complete, in others only small remains of islands exist.
26	9 10	4 months	Meat 1 month without glycosuria. Bread 6 weeks with glycosuria. Meat 2 weeks with glycosuria.	Islands almost gone; only small clumps of heavily granulated A cells and maximally vacuolated B cells remain.
22	10 11	4 months	Continuous program of protein-fat diet to verge of tolerance, and frequent glycosuria checked by fasting. Downward progress and terminal cachexia.	Slight diffuse fibrosis. Acini normal and well filled. Islands scarce and small, generally with swelling and vacuolation of most or all cells. Occasional small cell-groups are free from vacuolation, consisting probably of A cells.
28	10/11	6 $\frac{1}{2}$ mos.	Protein-fat. Glycosuria absent 3 months, slight 2 months, heavy 1 $\frac{1}{2}$ months.	Islands disappearing; nothing left but small groups of non-vacuolated or maximally vacuolated cells, crowded closely by acini on all sides. Vacuolation of cell-cords, and rarely of small ducts.
29	3 4	8 $\frac{3}{4}$ mos.	Overfed with protein and fat 8 months,	Islands entirely absent, except for rare

TABLE 2.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
			with frequent glycosuria checked by fasting. Finally continuous glycosuria 3 weeks and death in coma.	small groups of probable A cells. All degrees of zymogen content of acini. Some acini involuted, others strikingly vacuolated. Small ducts and cell-cords maximally vacuolated. Ganglia normal.
30	10/11	9½ mos.	Glycosuria absent on restricted diet 7 months, then continuous on regulated mixed diet 2½ months.	Swelling and vacuolation of a minority of island cells.
31	8/9	11 mos.	Diabetes controlled by restricted protein-fat diet about 9 months; then hyperglycemia developed, followed by glycosuria during the final week, also acidosis. Well nourished when killed.	Numerous large islands; a few cells in each show slight to maximal vacuolation.
32	13/14	11 mos.	Glycosuria kept absent on protein-fat diet for 10 months. Bread then failed to produce glycosuria. Addition of glucose then maintained glycosuria till appetite failed. Glycosuria slight or absent in final week.	Thinning of granulation or slight vacuolation in minority of island cells.

TABLE 2.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
33	7 8	17 mos.	Diabetes controlled by diet for 15½ months; then continuous glycosuria on mixed diet for 1½ months. Death in cachexia.	Much diffuse fibrosis. Acini irregular in size, form and fullness; considerable involution. In some areas islands are large, numerous, maximally vacuolated, in others only a few small remains are found.
34	12 13	2 years	Tolerance spared by restricted diets most of time. Hyperglycemia with frequent traces of glycosuria for about last month.	Remnant slightly sclerotic in gross; weight not diminished. Extensive interacinar fibrosis. Acini well filled. Islands abundant in number and size. Slight fibrosis in some, marked vacuolation in all.

TABLE 3.
Diabetes After Repeated Operations

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
1	15/16	3 days	Fasting. No glycosuria.	Grossly reddened, swollen and brittle. Interlobular septa hemorrhagic. Parenchyma takes pale stain everywhere and in some areas shows degeneration. Islands protected by internal position; no inflammation or vacuolation.
	1.3 gm. additional	7 days	Fasting with glycosuria.	Grossly, soft and lobulated. Parenchyma mostly normal. No vacuolation of islands.
	0.3 gm. additional	7 days	Fasting with glycosuria.	Pale staining and inflammation in some regions, others normal. Moderately advanced vacuolation of all islands.
2	20/21	4 days	Fasting with glycosuria.	Thinning of granulation in a few island cells.
	0.2 gm. additional	3 days	Fasting with glycosuria.	Slight vacuolation in a few island cells.
3	14/15	8 days	Pancreas operation performed after 13 days fasting. Fasting continued. No glycosuria, but hyperglycemia of 0.278 to 0.351%.	Slight vacuolation in majority of island cells.
	0.1 gm. additional removed	4 days	Fasting. Hyperglycemia without glycosuria.	Slight vacuolation in a minority of island cells, maximal vacuolation in a few.

TABLE 3.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
4	18/19	8 days	Oatmeal. Glycosuria.	Well marked vacuolation in a minority of island cells.
	0.3 gm. additional	10 days	Oatmeal. Glycosuria.	Slight to moderate vacuolation in islands.
	0.3 gm. additional	7 days	Oatmeal. Glycosuria.	Hypertrophy of remnant. Extreme vacuolation of all beta cells.
5	12/13	10 days	Bread. Glycosuria 2 days; suppressed by cachexia.	Normal. No vacuolation in islands.
	1 gm. additional	6 days	Bread. Slight glycosuria.	Normal. No vacuolation in islands.
6	9/10	10 days	Bread 1 week with glycosuria, then fasting 3 days without glycosuria.	Inflammation and fibrosis present in some areas, absent in most. Small ducts and cell-cords numerous. Islands few and small. Maximal vacuolation of a few cells; others appear normal.
	0.6 gm. additional	1 week	Meat. Glycosuria.	Inflammation and vacuolation both a little greater.
7	14/15	13 days	Fasting with moderate glycosuria.	Thinning of cytoplasm in most island cells, complete vacuolation of a few cells.
		3 days	Fasting with heavier glycosuria.	Slight advance of vacuolation, both in

TABLE 3.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
8				degree and in number of cells involved.
	6/7	2 weeks	Bread first week. Meat second week.	Broad bands of edematous fibrous tissue between lobules. Slight intralobular inflammation. Acini normal. Majority of island cells vacuolated, mostly to maximal degree.
	0.4 gm.	2 weeks	Fasting 10 days.	Trivial fibrosis. Islands reduced to a few small clumps of maximally vacuolated cells. A very few non-vacuolated cells.
9	15,16	2 weeks	Fasting and low diet to suppress glycosuria.	Normal parenchyma. Islands plentiful. No vacuolation.
	0.4 gm. additional	3 weeks	Bread diet; no glycosuria.	Hypertrophy of remnant from 2.2 to 6.1 gm. prevented diabetes. Parenchyma normal. Islands plentiful. Vacuolation absent or doubtful.
	0.7 gm. additional removed	3 months	Bread and glucose, then bread, then meat. Diabetes and fatal downward progress.	Islands have disappeared except for occasional small areas, evidently of A cells, with rarely a few vacuolated B cells. Parenchyma otherwise normal.

TABLE 3.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
10	15 16	2 weeks	Bread. Glycosuria diminished to zero.	Acini normal. Islands numerous, often irregular and non-capsulated as though new-formed. Thinning of granulation in island cells, rarely distinct vacuolation.
	0.25 gm. additional	1 month	Bread and glucose, then bread, then meat. Increasing severity of diabetes.	Slight fibrosis at margin. Acini irregular in form and fullness. Islands extremely scarce and small, consisting only of a few non-vacuolated and rare vacuolated cells (presumably A and B cells). Vacuolation in a few small ducts.
11	9 10	2 weeks	Bread and glucose. Slight transitory glycosuria.	Islands normal, without vacuolation.
	0.4 gm. additional	3 weeks	Bread and glucose. Slight transitory glycosuria.	Islands normal, without vacuolation.
	0.2 gm. additional	1 week	Bread and glucose. Slight transitory glycosuria.	Islands normal, without vacuolation.
	0.4 gm. additional	5 weeks	Bread diet with heavy glycosuria 4 weeks. Fasting and protein feeding without glycosuria during last week. Death from cachexia.	Islands reduced in number; maximal vacuolation in large minority of cells.

TABLE 3.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
12	19/20	3 weeks	Meat. Increasing glycosuria.	Moderate to advanced vacuolation in majority of cells of all islands.
	0.2 gm. additional	5 days	Fasting with glycosuria.	No change from preceding.
13	8.9	3 weeks	Bread. Glycosuria.	Normal parenchyma in some areas, interacinar pancreatitis in others. Islands abundant and large; slight vacuolation in majority of all cells, maximal in a few.
	1 gm. additional	2 weeks	Bread. Glycosuria.	Pancreatitis less. Islands large as before, similar numbers of cells affected, but vacuolation in these is now maximal.
	0.6 gm. additional	3 weeks	Bread. Glycosuria.	No important fibrosis. Islands disappearing; only a few small exhausted remains are found.
14	7/8	3 weeks	Diminishing glycosuria on bread and glucose diet, absent on last day.	Slight vacuolation of a few cells in a few islands.
	1.5 gm. additional	9 days	Meat diet. No glycosuria.	Normal. No vacuolation.
	1.8 gm. additional	11 months	Glycosuria prevented by restricted diet up to last	Vacuolation in a minority of island cells.

TABLE 3.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
15	3/4	3 weeks	month, when there was hyperglycemia and frequent glycosuria. Bread and glucose. Heavy exercise on treadmill. No glycosuria.	Normal.
	2.2 gm. additional	2 weeks	Bread and glucose. Given 200 gm. glucose by stomach tube 1 1/4 hour before operation. Transitory glycosuria.	Normal.
	1.2 gm. additional	2 weeks	Bread diet, with glycosuria.	Slight to moderate vacuolation of minority of cells in all islands.
	0.6 gm. additional	2 1/4 months	Protein-fat diet without glycosuria; then gain of 4 kgm. weight resulted in glycosuria 1 week before operation.	Vacuolation in a few cells of most but not all islands.
	1.4 gm. additional	2 days	Fasting with heavy glycosuria.	Possible advance of vacuolation, not positive.
16	7/8	24 days	Intermittent glycosuria on bread and glucose.	Islands large and numerous; rare cells swollen and vacuolated.
	1.4 gm. additional	7 months	Glycosuria brought on by fattening on protein-fat diet after 6 months, then continuous for 1 month. Death in coma.	Islands normal in number and size; half or more of the cells widely swollen and vacuolated.

TABLE 3.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
17	11/12	1 month	Bread diet, with glycosuria first two weeks, none thereafter.	Rare islands contain 1 or 2 maximally vacuolated cells. Otherwise normal.
	0.75 gm. additional	6 weeks	Bread diet 2 weeks with glycosuria, thereafter protein-fat with glycosuria and acidosis.	Islands plentiful and large with maximal vacuolation in almost all cells. Some vacuolation of cell-cords.
18	Splenic process, 1/3 of pancreas	5 weeks	Bread. No glycosuria.	Normal.
	Uncinate process, 1/4 of pancreas	5 months	Same.	Normal.
	Splenic end of body, 1/4 of pancreas	6 months	Bread and glucose. No glycosuria.	Normal.
	1.25 gm. additional	5 months	Bread. No glycosuria.	Normal.
	0.85 gm. additional	4 months	Mixed diet, partly with glucose. No glycosuria.	Normal.
	0.8 gm. additional	3½ years	Diabetes absent 3 years on restricted protein-fat diet. Fattening gradually brought on by hyperglycemia and glycosuria. Fasting 3 weeks failed finally to stop glycosuria.	Acini vary from full to involuted. Only a few small islands remain, with maximal vacuolation in most cells.
19	11/12	6 weeks	Glycosuria generally absent, but present with glucose feed-	Rare islands contain 1 or 2 vacuolated

TABLE 3.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
			ing during last week.	cells; others normal.
	0.2 gm. additional	1 month	Bread and glucose diet. Glycosuria present 3 weeks, absent last week.	No clear vacuolation, but thinning of granulation in considerable proportion of cells of majority of islands.
	0.6 gm. additional	7 months	Glycosuria absent 6 months on protein-fat diet, finally brought on by excess of fat; suppressed by fasting, but hyperglycemia continuous for last month.	Islands as numerous as before. Vacuolation involves about the same proportion of cells, but is more advanced, often maximal.
20	Uncinate process, 14 of pancreas.	6 weeks	Bread. No glycosuria.	Normal.
	Splenic process, 13 of pancreas.	11 months	Bread, with glucose for considerable periods. No glycosuria.	Normal.
	4.75 gm. additional	17 months	Bread. No glycosuria.	Normal.
	1.8 gm. additional	1 month	Bread. No glycosuria, though dog is potentially diabetic as shown by glucose tests.	Incipient vacuolation in a few cells of a few islands.
	0.6 gm. additional	3 weeks	Bread, without glycosuria. Dog is potentially diabetic, shows heavy gly-	Slight vacuolation in large proportion of island cells.

TABLE 3.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
21	9/10	3½ months	cosuria when given glucose on a few occasions. Glycosuria most of time on bread diet, stopped occasionally by fasting or reduced diet.	Only last remains of maximally vacuolated islands are present.
	0.2 gm. additional	5 days	Fasting. Glycosuria stopped probably by cachexia.	No change from preceding.
22	8/9	5½ months	Marked tendency to diabetes, checked by restricted protein-fat diet, except on occasional test days.	Normal.
	0.1 gm. additional	1 week	Meat and milk diet. Hyperglycemia without glycosuria. Cachexia.	Very slight vacuolation in islands.
23	5/6	5¼ months	Bread and glucose. Occasional glycosuria.	Slight vacuolation of a few island cells.
	1.3 gm. additional	1 year	Protein-fat diet, without glycosuria. Dog gradually became obese. During last 2 weeks, bread diet with hyperglycemia, no glycosuria.	Slight vacuolation of a few island cells.
	0.4 gm. additional	3¼ months	Weight reduced by fasting and low protein diet. Glycosuria absent on bread. Frequent	Maximal vacuolation of 1 or 2 cells in most islands. Islands otherwise normal.

TABLE 3.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
			slight glycosuria from glucose addition during last 3 weeks.	
	0.2 gm. additional	3 weeks	Bread and glucose diet, with slight glycosuria.	Larger numbers of swollen and vacuolated island cells. Slight fibrosis invades some islands, which show appearances resembling "atrophy" of human islands.
	0.8 gm. additional	5 days	Fasting without glycosuria. Death from cachexia.	Appearance of "atrophy" as before. Vacuolation perhaps a little less.
24	8.9	7 months	First protein, later mixed diet, later (2 weeks) addition of 100 to 400 gm. glucose daily, without glycosuria.	Islands numerous, large, normal, without vacuolation.
	0.9 gm. additional	1½ months	Heavy glycosuria and acidosis on mixed diet. Death in coma.	Islands numerous and large as before, with maximal vacuolation of great majority of cells.
25	8.9	8 months	Glycosuria absent on protein diet 7 months, present on mixed diet 1 month.	Islands maximally vacuolated in some areas, disappearing in others. No duct vacuolation.
	1.2 gm. additional	5 days	Protein-fat, with glycosuria.	Islands as before. Vacuolation in some ducts.

TABLE 4.
Severe Diabetes Controlled by Diet

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
1	23/24	2 days	Fasting. No glycosuria.	Interlobular septa greatly swollen, full of fibrin, red corpuscles, leukocytes and round cells. A few small patches of degeneration in parenchyma, invaded by leukocytes. Acini take pale stain, vary from full to empty; some involuting. Islands free from invasion or vacuolation though many are pale.
	0.8 gm. additional	10 days	Pure fat. No glycosuria.	Some areas of inflammatory reaction and pale staining. Parenchyma mostly normal. No change in islands.
2	20/21	8 days	Fasting, without glycosuria.	Acini normal. Islands plentiful; granulation thinned in numerous cells, but no vacuolation.
	0.5 gm. additional	5 days	Same.	Some marginal and interlobular bands of hemorrhagic fibrous tissue. Acini normal. Islands plentiful; thinning of granulation in a few cells; no vacuolation.
	0.15 gm. additional	12 days	Same.	Hypertrophy of remnant from 1.4 to 2.5

TABLE 4.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
				gm. Marginal fibrosis, subdividing but not invading parenchyma. Acini normal except for irregularity of size and form. Islands free from vacuolation.
3	14/15	9 days	Fasting. Glycosuria 3 days, then negative.	Vacuolation in islands doubtful or absent.
4	7/8	12 days	Bread diet, with continuous but diminishing glycosuria.	A few cells in every island show moderate to maximal vacuolation.
5	28/29	20 days	Bread at first, later meat. Glycosuria continuous for first eight days, then suppressed by cachexia.	Vacuolation doubtful.
6	12/13	3 weeks	Meat diet 1 week without glycosuria. Bread 1 week with glycosuria, then 1 week without glycosuria.	Normal.
7	12/13	3½ weeks	Protein-fat diet, with continuous undernutrition necessary to maintain sugarfreedom. Death finally from inanition.	Islands scarce and small. No vacuolation.
8	12/13	8 months	Bread diet. Extreme emaciation and cachexia. No glycosuria.	Normal.

TABLE 4.
(Continued)

Dog No.	Portion of pancreas removed	Interval since operation	Diet and other details	Pathology of pancreas remnant
9	9/10	9 months	Glycosuria was possible at all times on bread feeding, but except for a few test days it was kept continuously absent by meat diet.	Parenchyma normal except for a few broad bands of fibrous tissue. No vacuolation.
10	7/8	10 mos.	Carbohydrate overfeeding and glycosuria 6 weeks. Protein-fat without glycosuria 6 months. Protein-fat with glycosuria 6 weeks. Fasting, low diet and cachexia without glycosuria 1 month.	Islands noticeably scarce, but without vacuolation.
11	11/12	1 year	Protein-fat diet and undernutrition, controlling glycosuria.	Islands rather scarce and small, but free from vacuolation.

NOTES ON THE FIGURES.

The appearances in the hydropic degeneration of experimental diabetes in dogs can best be made clear by reference to the figures, which are arranged to show the successive steps of the change. The technic was the usual fixation of absolutely fresh tissue in Zenker fluid (generally with only 2 per cent acetic acid) and staining of 3-micron sections with methylene blue and eosin.

Fig. 1 shows 2 islands which might be passed hastily as normal, but which show incipient vacuolation especially in the form of thinning of cytoplasm. Still slighter degrees of the change than this are recognizable by an experienced observer. In special granule stains the same thing is seen in the form of a thinning of granules.

Fig. 2 shows a more advanced stage of thinning of cytoplasm. Also one cell near the lower left corner of the island is fully vacuolated and the nucleus is already becoming pyknotic. Instead of the gradual general thinning of cytoplasm, it is equally possible in animals for one or a few cells to blaze out with maximal vacuolation while the great majority retain strictly normal appearance, giving pictures identical with those shown in human tissue in figures 1 to 3 of paper 7. No reason for this different behavior of different cells or different islands has been found in the diet, the clinical course of the diabetes, the position of cells in the island, or any other known factor.

Fig. 3 is similar in appearance, but shows what is sometimes found when a rapidly advancing diabetes is checked by a sharp cut in diet. There is no positive proof whether the island cells have been vacuolated to a greater extent than this and are recovering granulation, or whether the vacuolation has merely been halted at this intermediate stage. But it is a general rule that cells are never swollen to their maximum until they have lost all or practically all visible cytoplasm. In this figure are seen a few cells which are maximally swollen but yet contain appreciable amounts of cytoplasm, and the assumption therefore is that these cells have been completely exhausted but are regaining their granulation and will presumably later regain their contour. In other words, such occasional findings render it probable

that extremely vacuolated cells can still recover if the cell membrane has not burst or if the nucleus is not too badly degenerated.

Fig. 4 shows the extreme swelling of certain island cells, so that they look almost like cells of adipose tissue, while most of the other cells are changed to a far less degree and some are still normal in appearance.

Figs. 5 and 6 show nearly maximal vacuolation of entire islands. In the central portion in each instance are seen cells which are little if at all changed. Under the special granule stains the majority of such cells are found to be alpha cells. The others are beta cells which for some reason survive longer than the others.

Fig. 7 is taken from a cat, while all the others of the series are from dogs. It gives a low-power view at the pinnacle of the vacuolation, when the islands are maximally exhausted and are possibly also hyperplastic but have as yet lost no cells.

Fig. 8 is a low-power view from a dog at a slightly more advanced stage. Islands are still present in fair numbers but distinctly diminished size. As the islands shrink by loss of degenerated cells, the acinar tissue closes in smoothly about them. Apparently the dissolving cells give off no toxic substance to create irritation. There is no connective tissue reaction, and not even a leukocyte comes to devour the debris. This is in radical contrast to what happens when acinar cells are destroyed. It may suggest a possible hope that an extract prepared solely from island cells may be non-toxic.

Fig. 9 shows an island in a similar stage under higher magnification. The group of unchanged alpha cells is as distinct as though a special granule stain were used.

Figs. 10, 11 and 12 give other views of disappearing islands. Fig. 12 shows a phenomenon which is not uncommon at just the right stage, namely the vacuolation of island cells scattered singly or in groups of 2 or 3 in or between the acini. According to Bensley's investigation these scattered individual cells need not be considered as remains of islands, but were probably either present originally in these locations or formed there from ducts under the stress of the functional need. They are picked out by the hydropic change more plainly than by a special stain, for they are easily recognizable under low power.

Fig. 13, from a dog which died in coma (dog B2-80) illustrates the end result of hydropic degeneration, when the entire pancreas may be searched thoroughly and not a single island found. The dog's deceptive appearance of health is shown in Fig. 7 of paper 5 of series 1⁵. Beta cells have entirely disappeared, and the small groups of alpha cells no longer resemble islands and are hard to find even under high magnification.

Fig. 14 shows a group of supposed alpha cells under the routine stain. These surviving groups are seldom as large as this, and often consist of only 1 or 2 cells. With the ordinary stains therefore they are indistinguishable from duct cells, but the granule stains furnish the proof that the alpha cells survive in this manner. (See paper 2). No matter how small the pancreas remnant or how severe or prolonged the diabetes, the alpha cells seem never to disappear or show visible evidences of overtaxed function.

Fig. 15 shifts the study to the duct cells. In the earlier stages of experimental diabetes they remain normal. In Fig. 4, between the two islands and to the right, one of the cell cords described by Bensley is rather indistinctly shown, and is composed of normal cells. These cords have not the lumen or connective tissue coat of ducts. In figures 8 and 10 are small ducts, the epithelium of which is normal and not vacuolated. Vacuolation of duct cells seems to vary in time and conditions. In some animals it begins shortly before the beta cells disappear; in others it may be missed even at later stages; and it is never present except with extreme and prolonged diabetes, so that many autopsies may be done before it is found. As this phenomenon has not been described before, several figures are devoted to it. It involves only the cell cords and small ducts, never the cylindrical epithelium of the large ducts. Fig. 15 shows a small duct, the cells of which are partly vacuolated, opening into a larger duct, the cells of which are not vacuolated.

Fig. 16 shows the last remains of an island, with a few maximally vacuolated and disintegrating beta cells and apparently a few surviving alpha cells. Above it is a small segment of a cell cord composed of completely vacuolated cells. These cells are distinguished from beta cells by their small size, which never becomes swollen, and also by the fact

that they seem never actually to degenerate or disintegrate, but can apparently persist in this vacuolated state indefinitely.

Figures 17 and 18 show other vacuolated cell strands. The small ducts were also vacuolated but are not shown in the picture. In Fig. 12 are also seen some vacuolated strands (especially to the left of the island in the lower center), and the small ducts (one in the upper right corner, and the other to the left of and above the island mentioned) contain partial vacuolation which is not clearly shown. In both Fig. 12 and Fig. 17 there is a tendency for the cell strands to broaden out into island-like areas, which are always distinguishable from the remains of true islands by the character of the cells and the absence of a capillary and trabecular framework.

Fig. 19 furnishes evidence that both the cell strands and the broader areas stand in relation to the duct system. Here a duct is seen connected with one of the usual long narrow cell cords on one side and with an irregular heap of cells on the other. The cells in this animal are only partly vacuolated.

Fig. 20 shows one of the typical "heaps" of vacuolated cells of pseudo-island contour. Fig. 21 shows a large irregular accumulation of such cells (which may actually have grown into the site of an old island, as indicated by the presence of a few maximally vacuolated beta cells) and also smaller vacuolated strands.

The wealth of small ducts and of cell-cords and cell-heaps in certain cases of prolonged severe diabetes point to an abundant and abnormal formation of these structures, presumably by proliferation from ducts. As mentioned in paper 6 and elsewhere, there is evidence that in partially depancreatized animals, in a border-line state or in the earlier stages of diabetes, a genuine new formation of islands is possible by duct proliferation. But when all beta cells, new and old, are exhausted, it is evident that the regenerative power has also been exhausted and no further production of island cells is possible. This may possibly mean that only certain cells in the ducts are capable of forming island cells, or the productive power may conceivably be limited for some other reason. A stimulus to proliferation seems still to exist, but this calls forth only a multiplication of duct cells. To this extent the process may be comparable to the proliferation of bile ducts after some liver necroses⁶, as if in an abortive attempt to

form liver cells. There is no proof as to whether the vacuolation indicates an internal secretory function of the small duct cells. Inasmuch as they show no granulation suggestive of an internal secretion with the Bensley staining methods, and also appear to suffer no further changes or degeneration in the further course of the diabetes, it may be more probable to interpret the phenomenon as exhaustion of a proliferative rather than of an endocrine function, the only reaction to the proliferative stimulus being then an over-production of functionless cells poor in cytoplasm. In defense of the opposite view may be urged the fact that a dog remains very different from a totally depancreatized dog even when possessing only a sclerotic pancreas remnant in which very little can be discovered except scar tissue and ducts.

There is some evidence of new formation of island tissue in the earlier stages of human diabetes, and convincing indications that this power is lost in the extremely severe stage; but neither vacuolation of ducts nor formation of the abnormal strands and heaps of cells has ever been observed in a human case, unless the "pseudo-islands" sometimes found (cf. paper 7) may be considered analogous.

SUMMARY AND CONCLUSIONS

1. The hydropic degeneration of the islands of Langerhans is proved to be a specific diabetic phenomenon, produced solely by over-strain of the function of the cells by diets in excess of the weakened assimilative power.

2. The rate of the anatomic change varies with the clinical condition, but with unchecked severity of diabetes a period of 4 to 7 days is generally required for development of the first positive vacuolation; maximum vacuolation may be attained in about a month; and in 6 weeks to 2 months all beta cells may have disappeared from the pancreas.

3. The hydropic change is probably reversible within certain limits, and even widely vacuolated cells may probably recover their former size and granulation provided the cell membrane has not burst or the nucleus become too badly degenerated.

4. The formation of numerous strands and heaps of duct cells, and the vacuolation of these and the epithelium of the smaller ducts, are described for the first time in the end stages

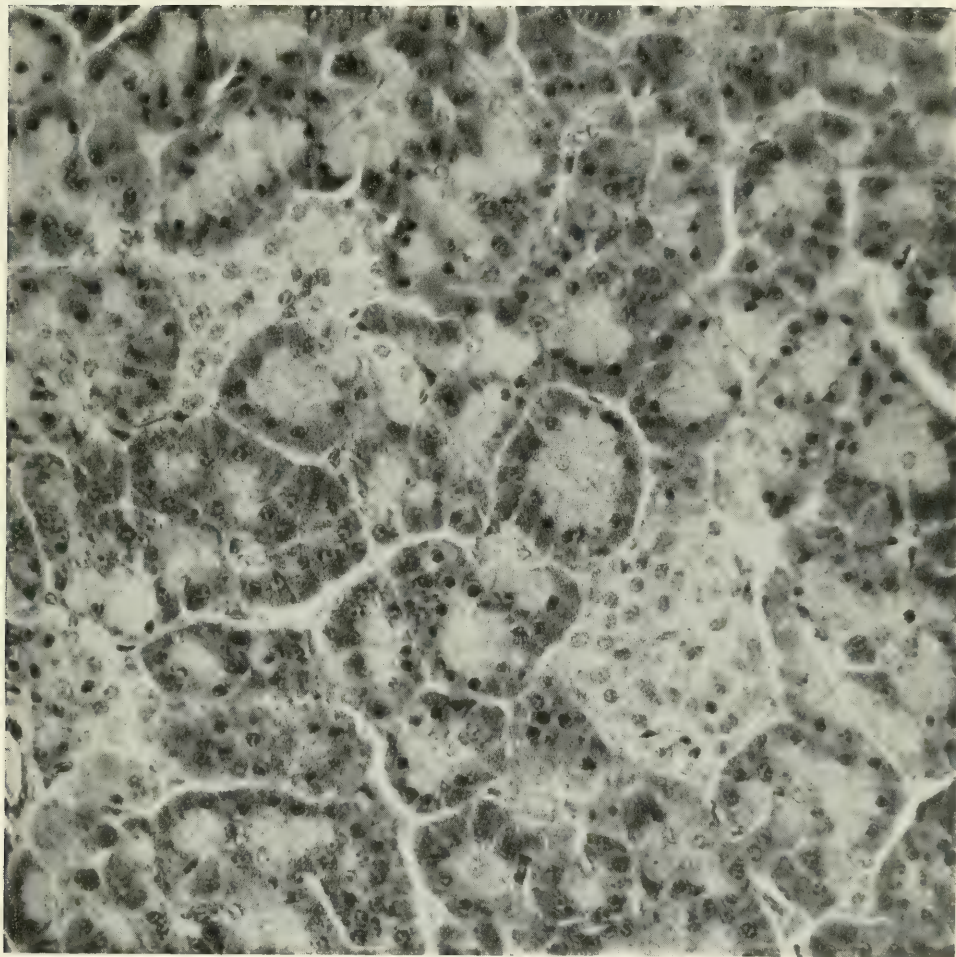


FIG. 1.

× 440.

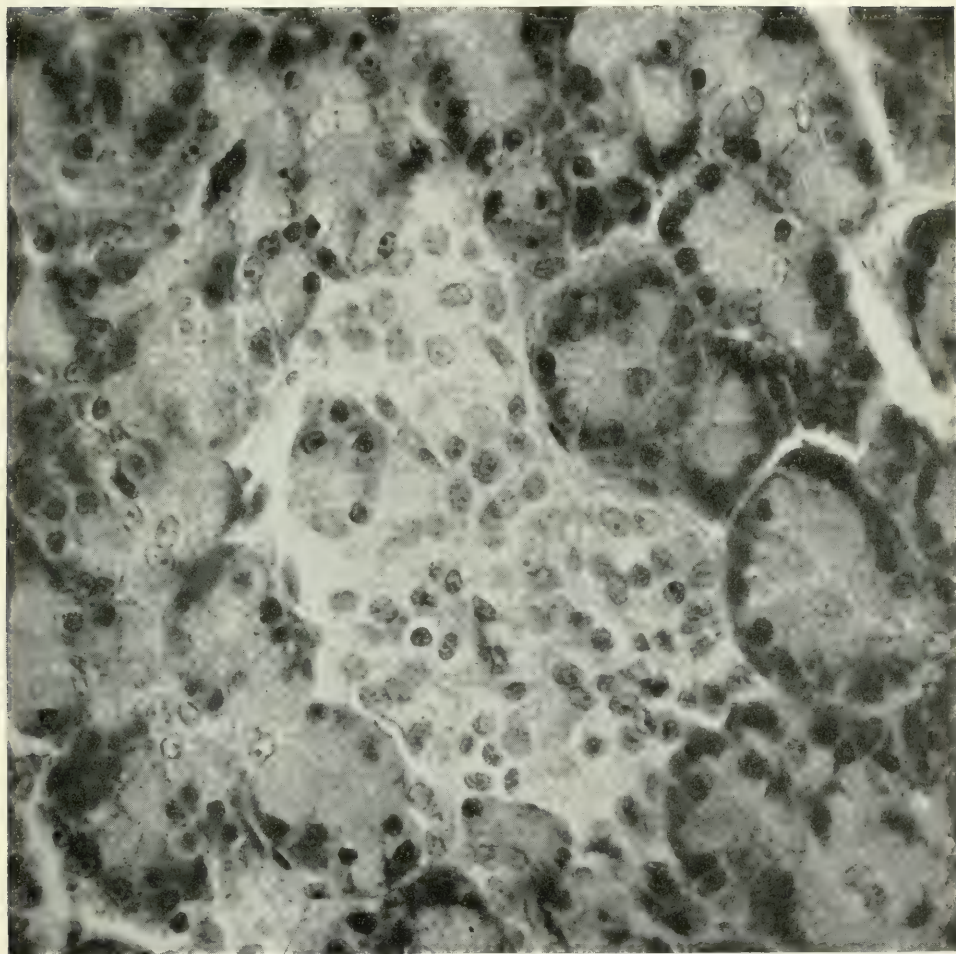


FIG. 2.

× 720.

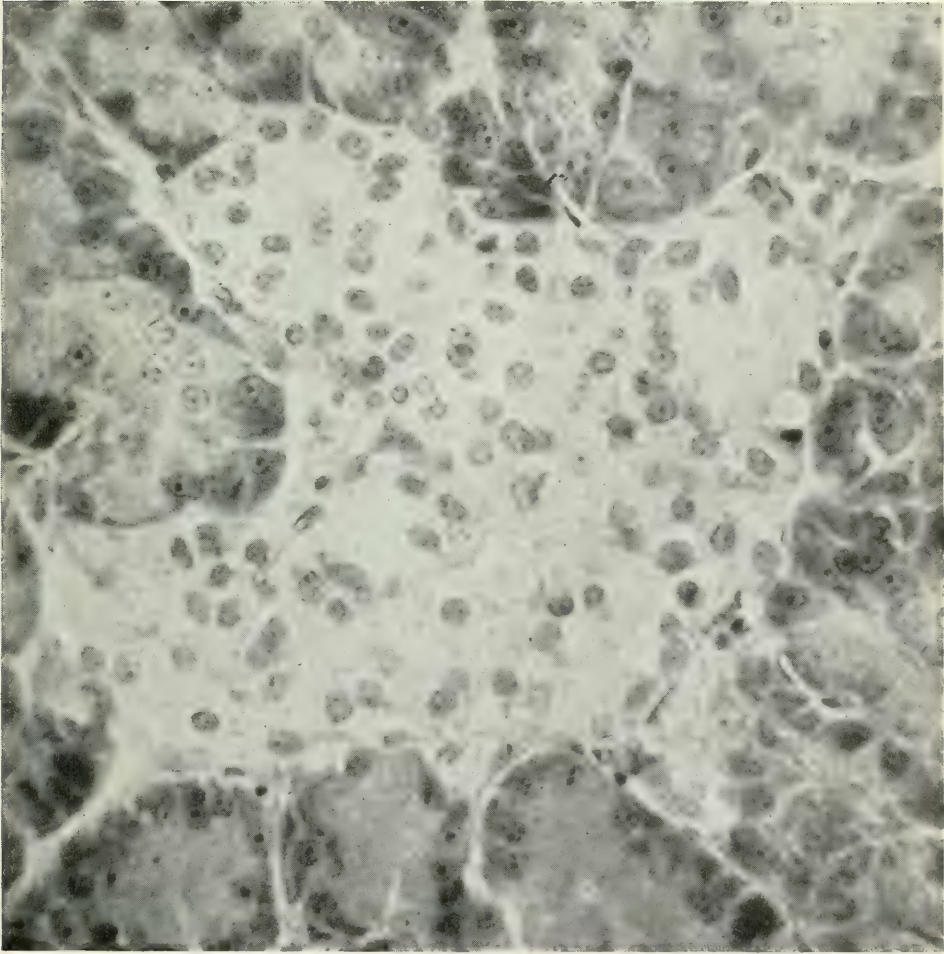


FIG. 3.

× 720.

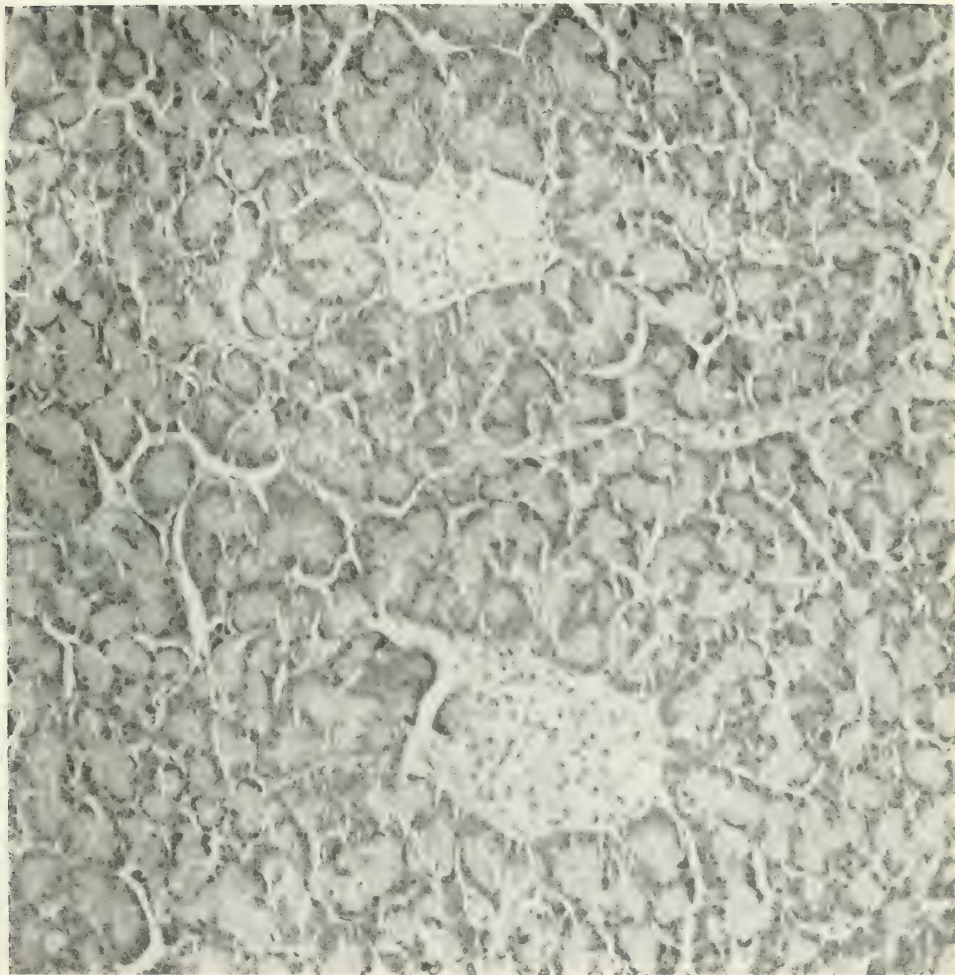


FIG. 4.

× 240.

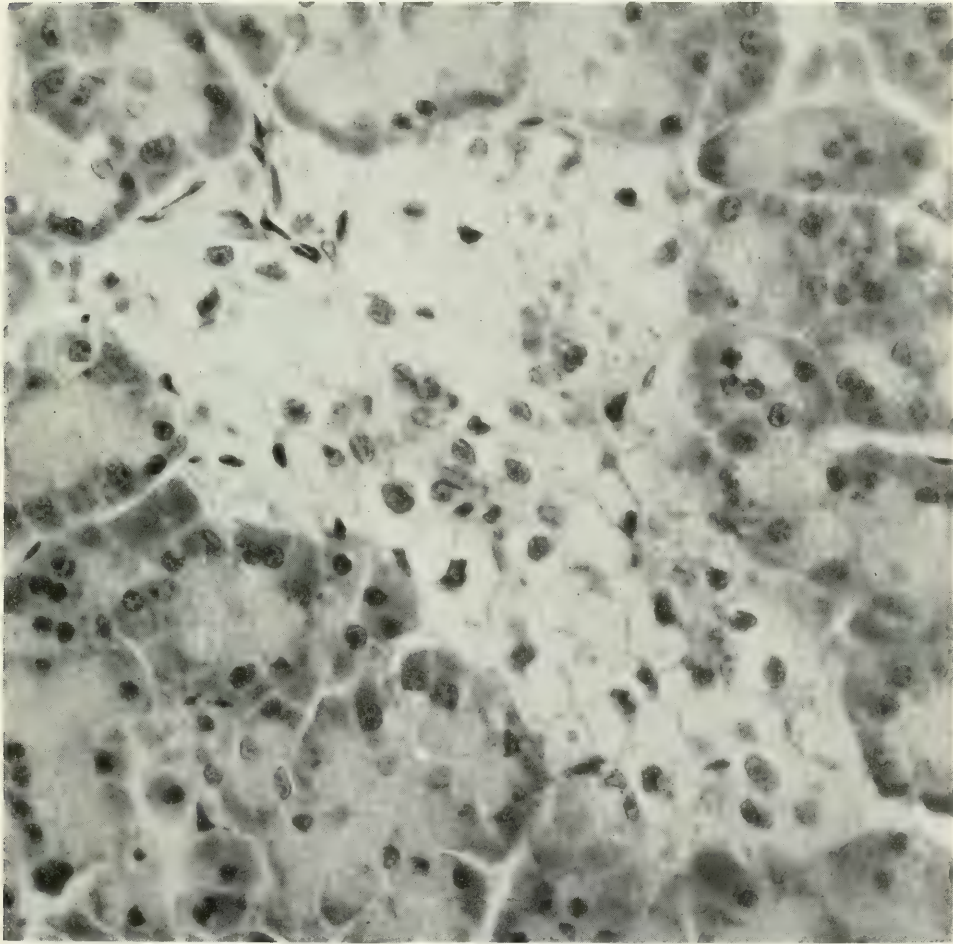


FIG. 5.

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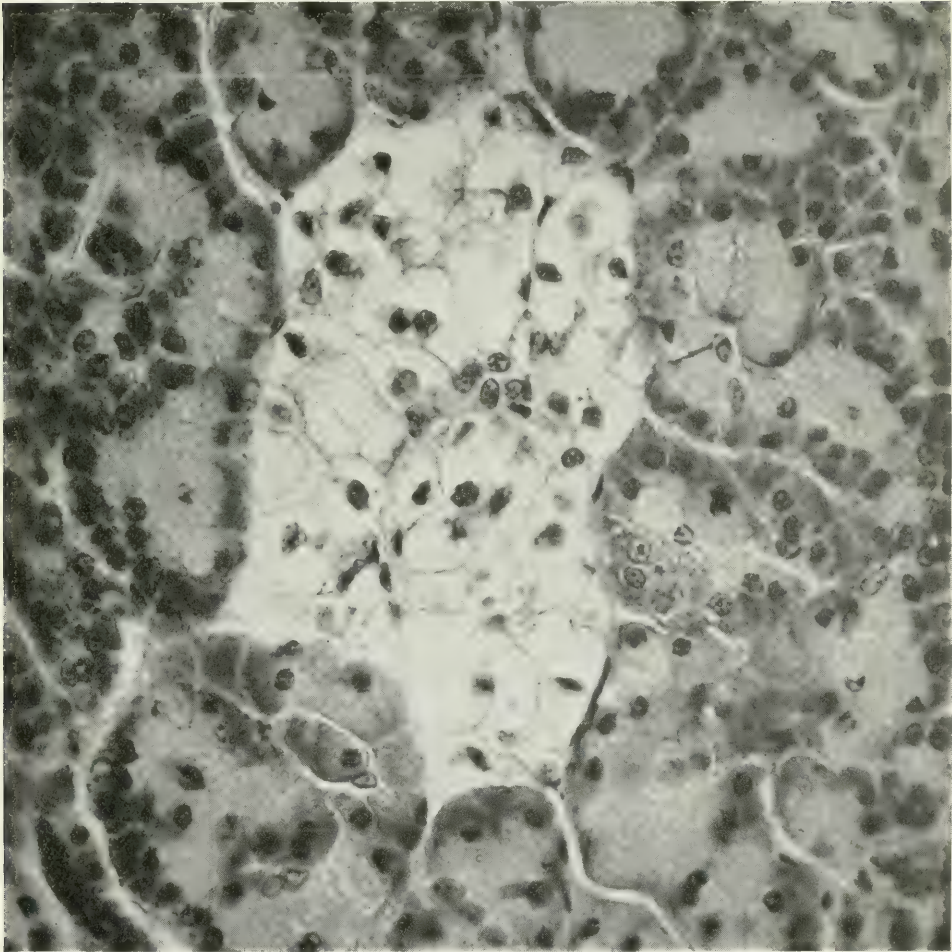


FIG. 6.

× 720.



FIG. 7.

× 82.

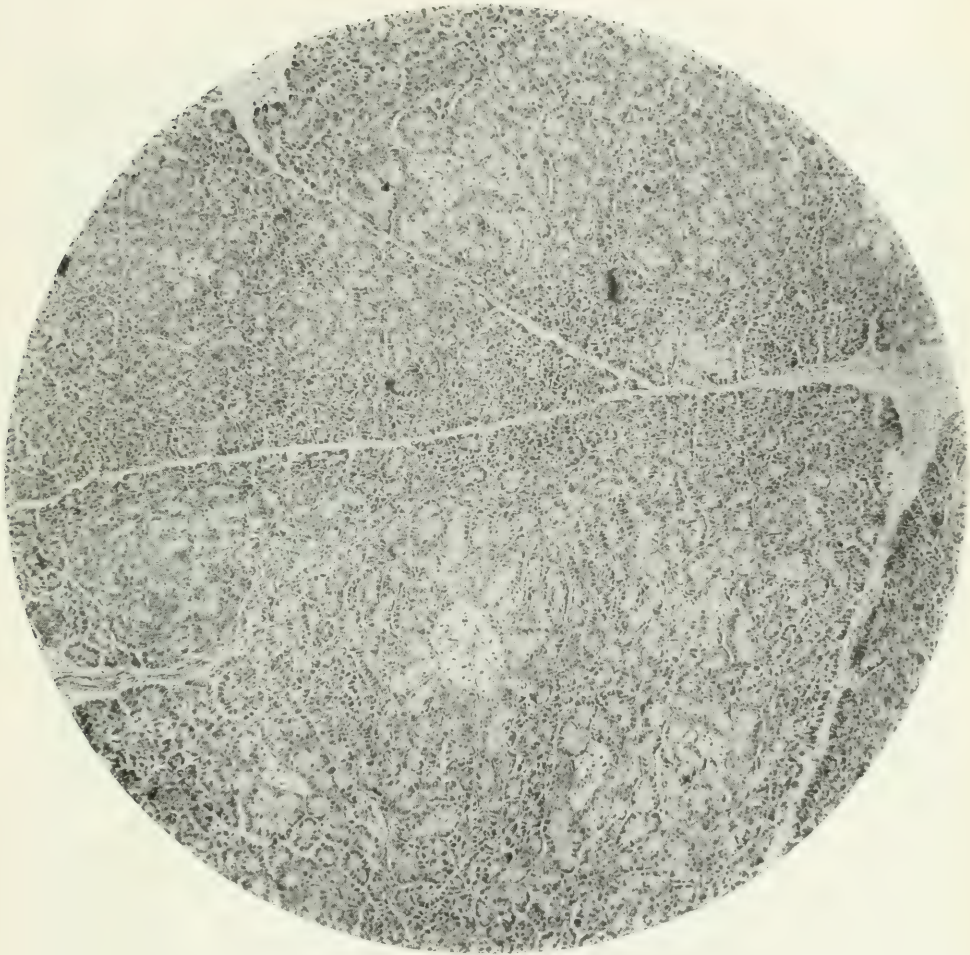


FIG. 8.

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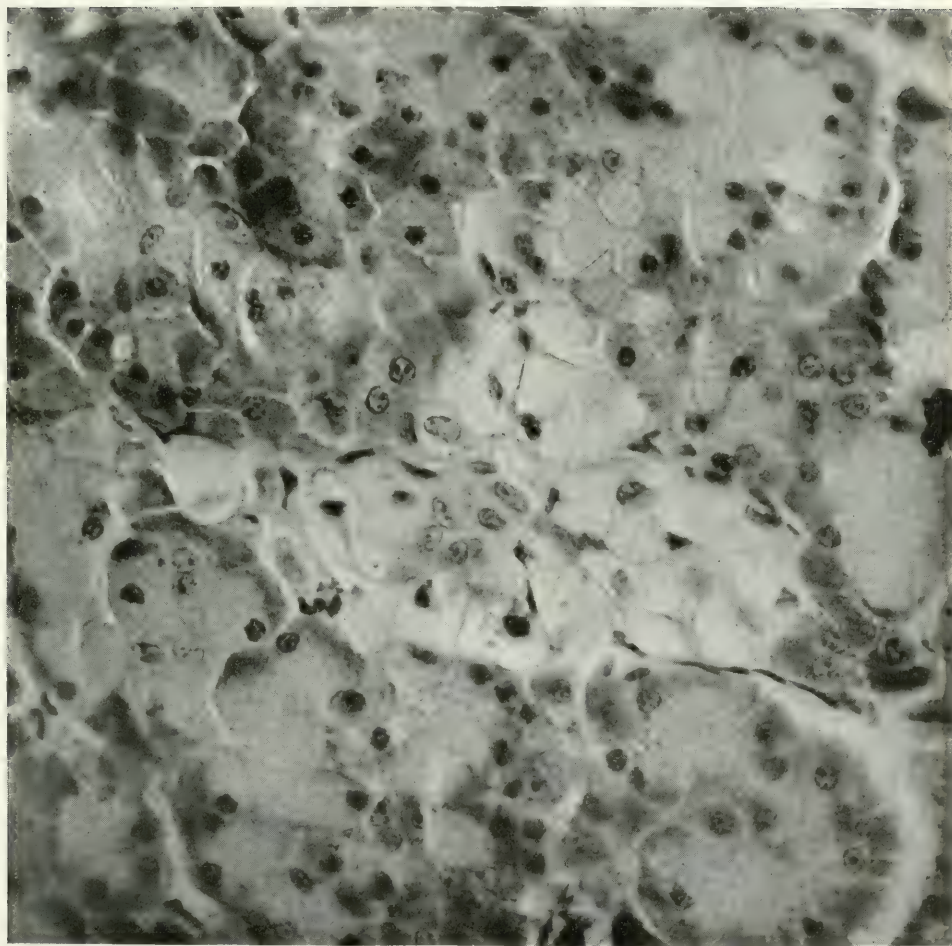


FIG. 9.

× 720.

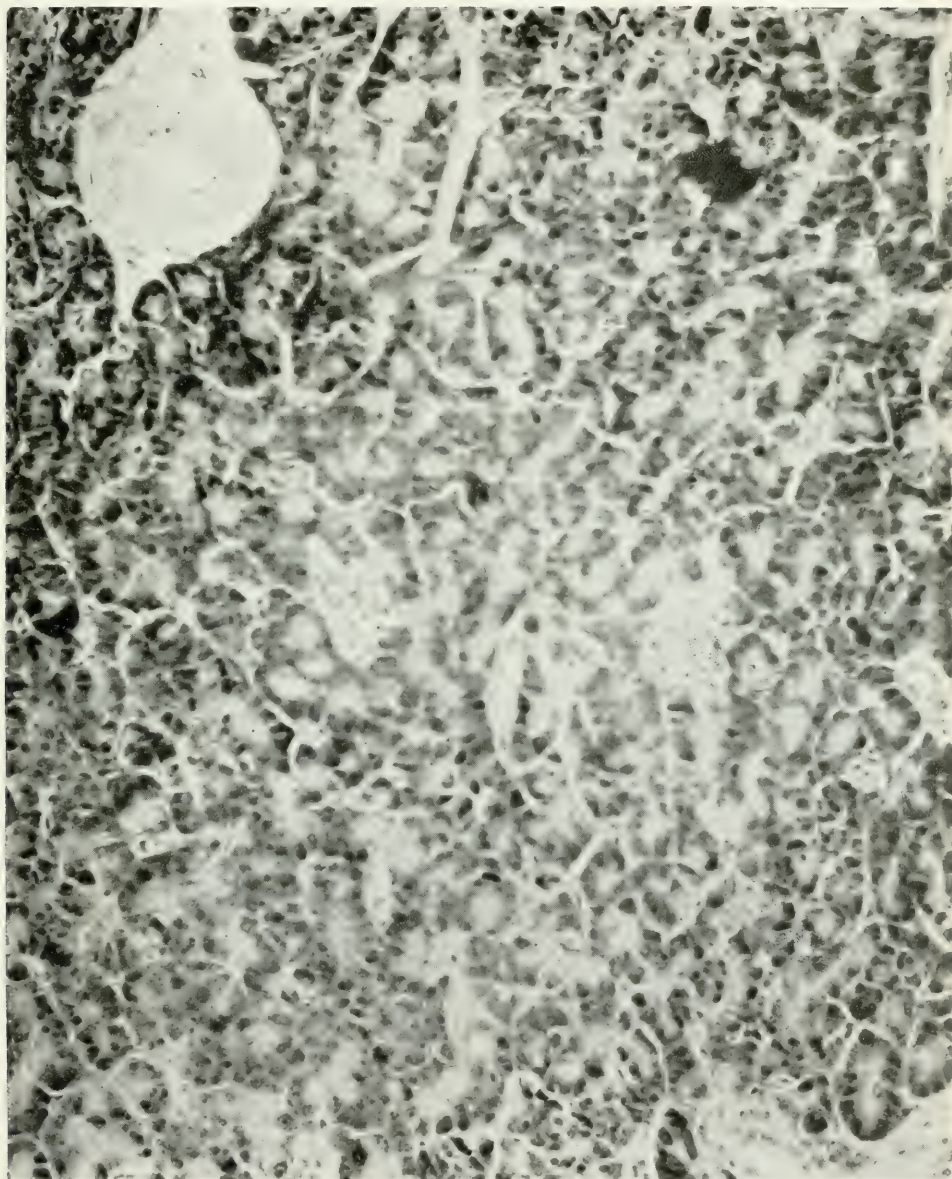


FIG. 10.

× 240.

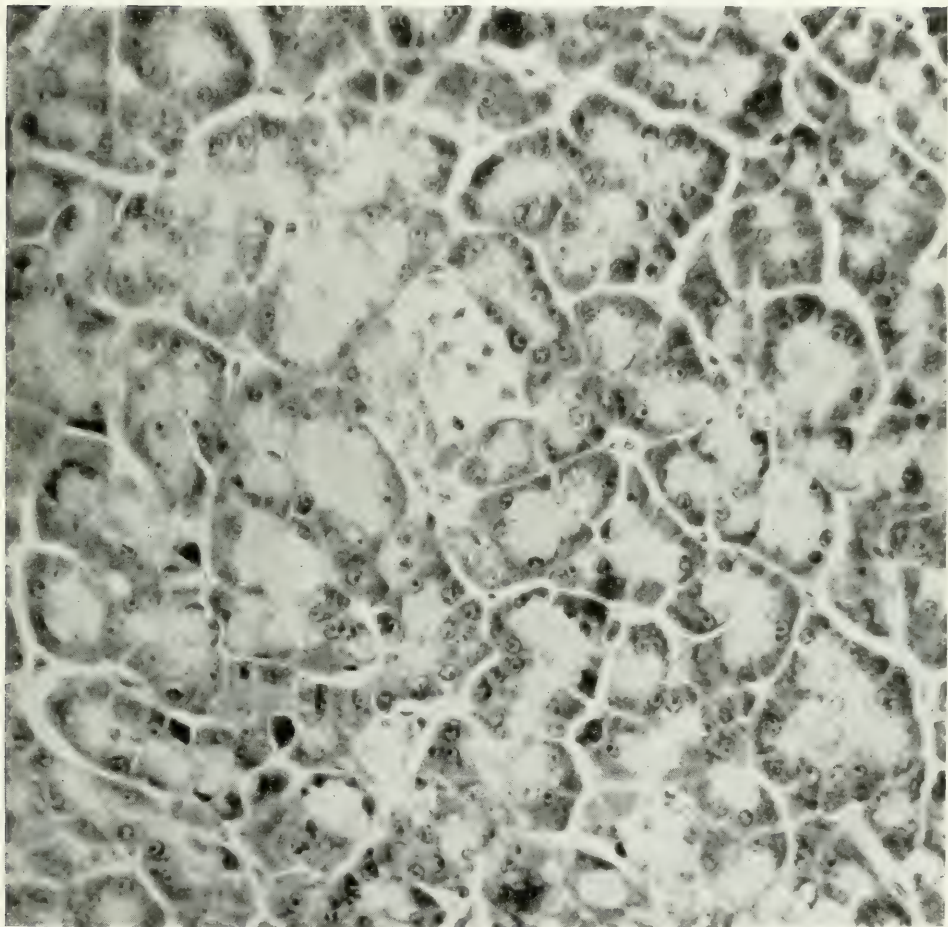


FIG. 11.

× 440.

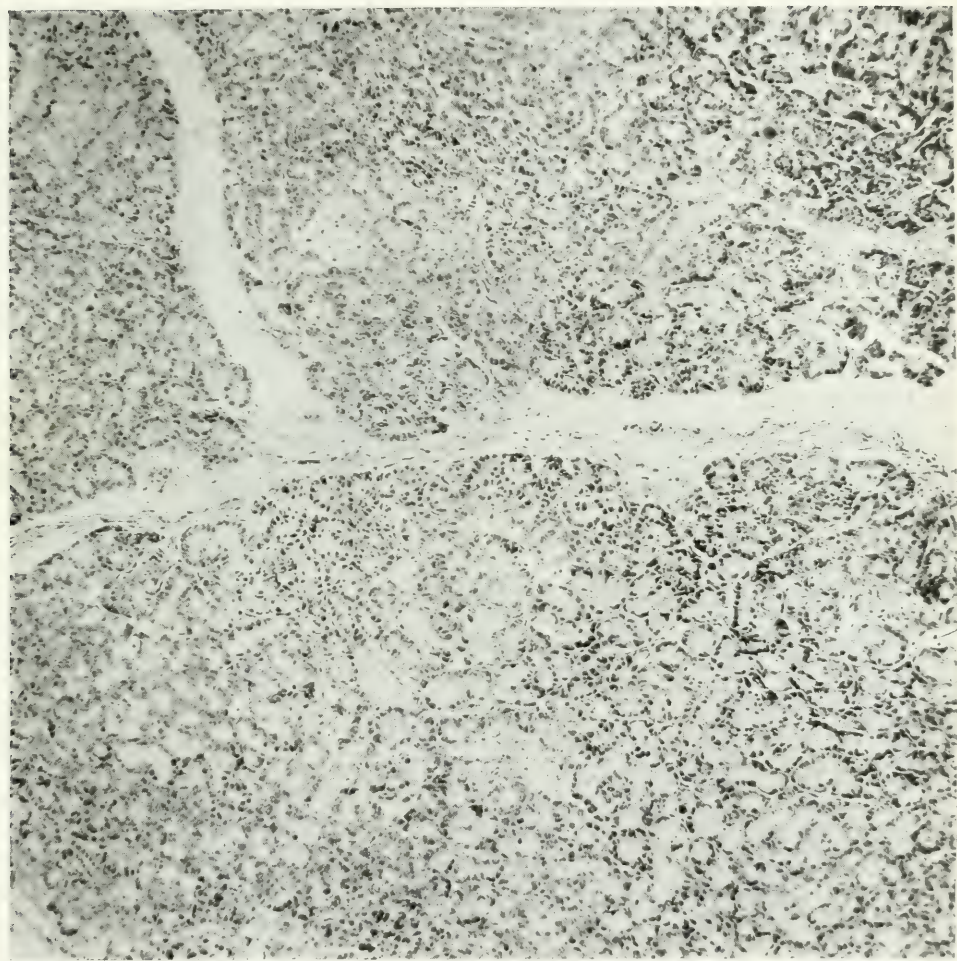


FIG. 12.

× 140.



FIG. 13.

× 80.

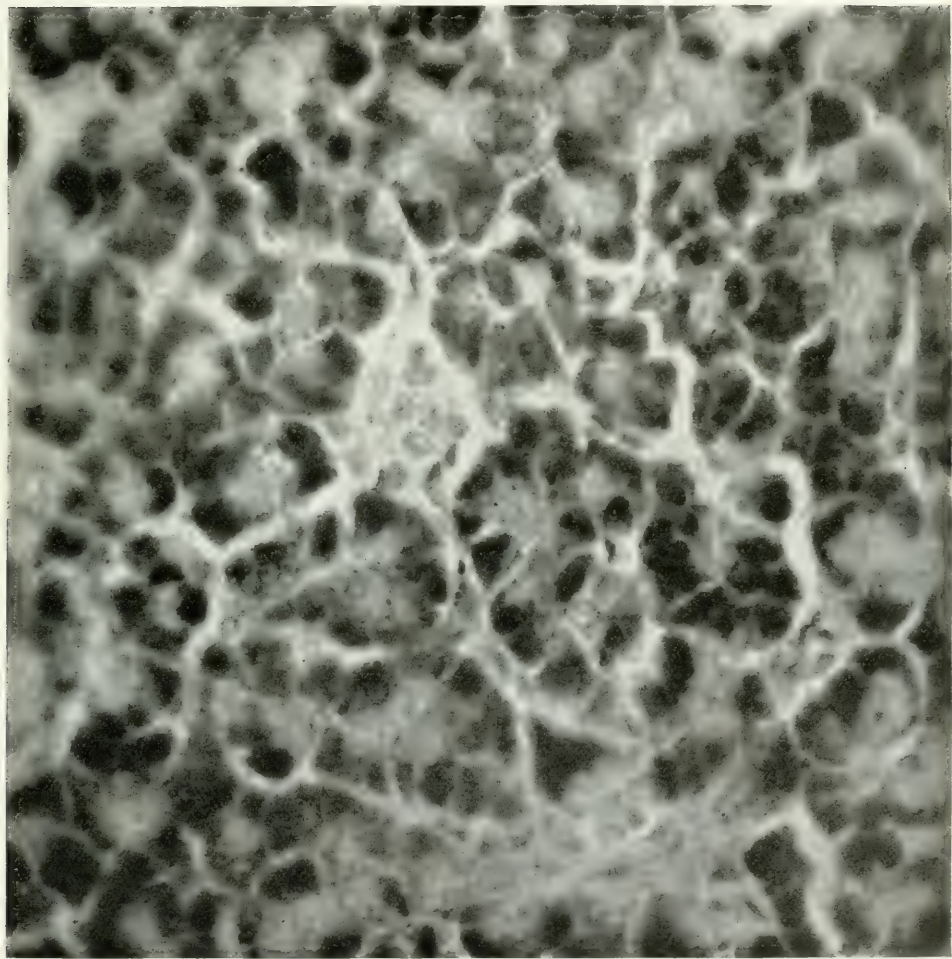


FIG. 14.

× 700.

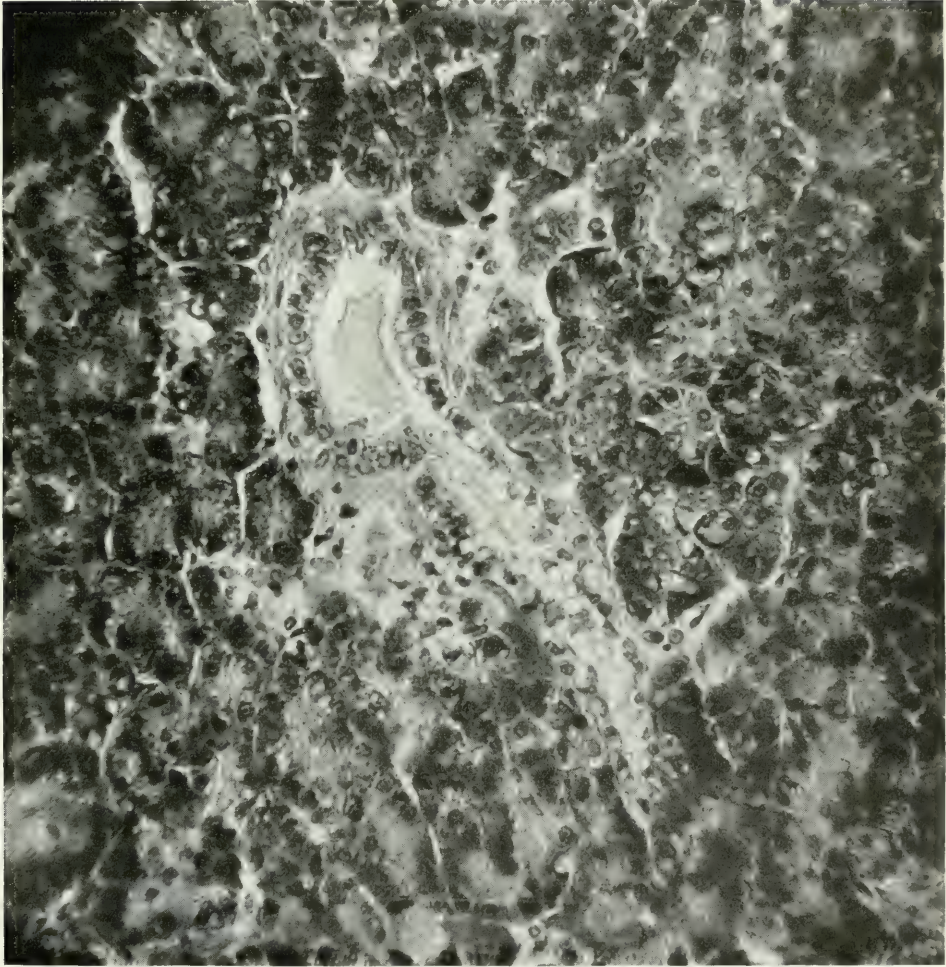


FIG. 15.

× 700.

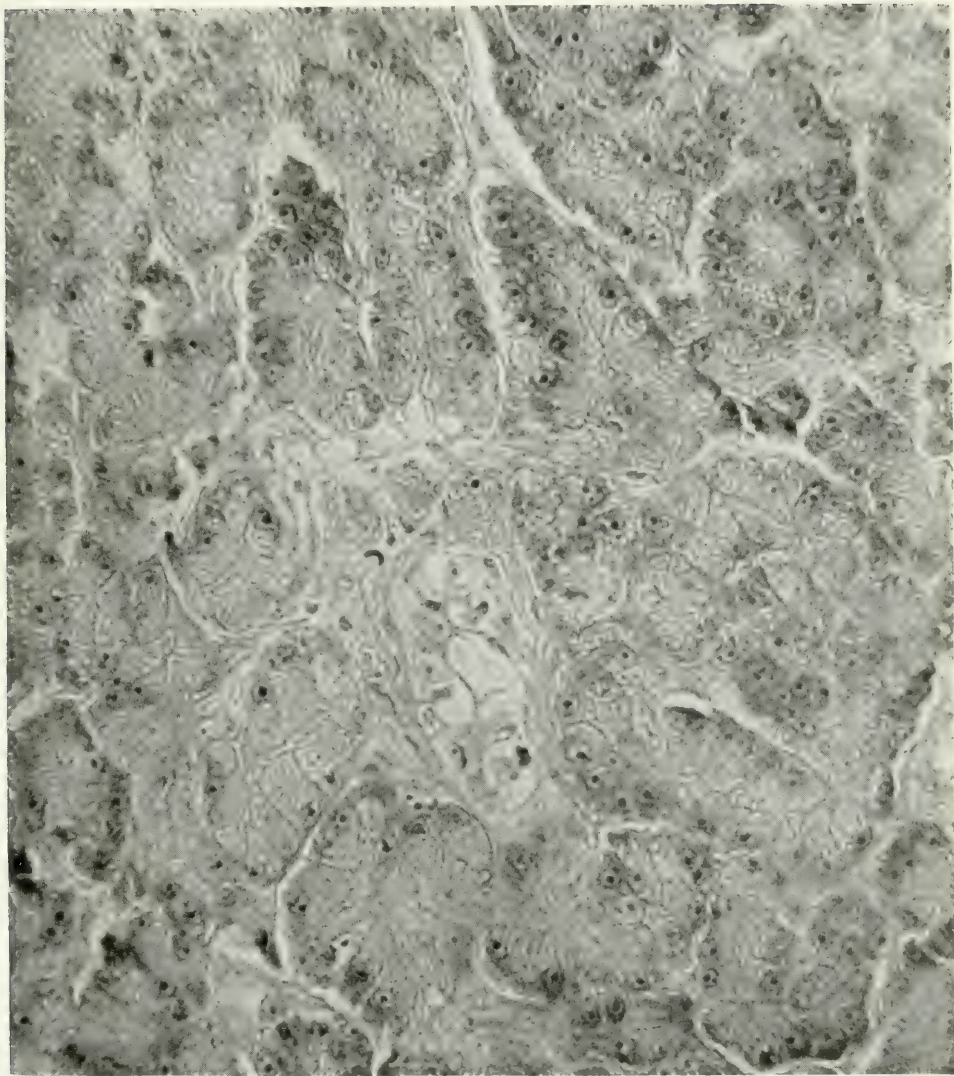


FIG. 16.

× 400.

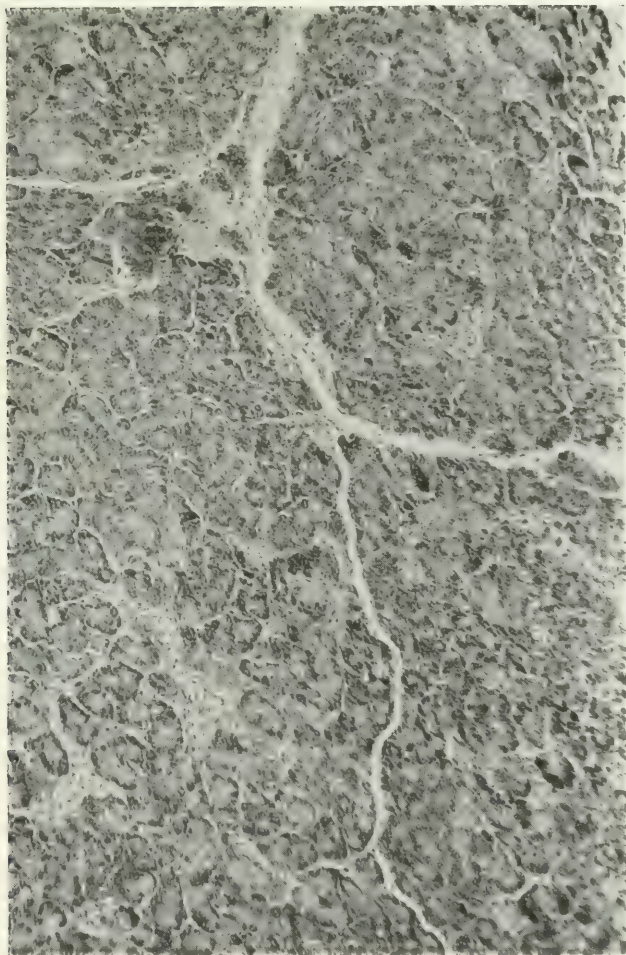


FIG. 17.

× 700.

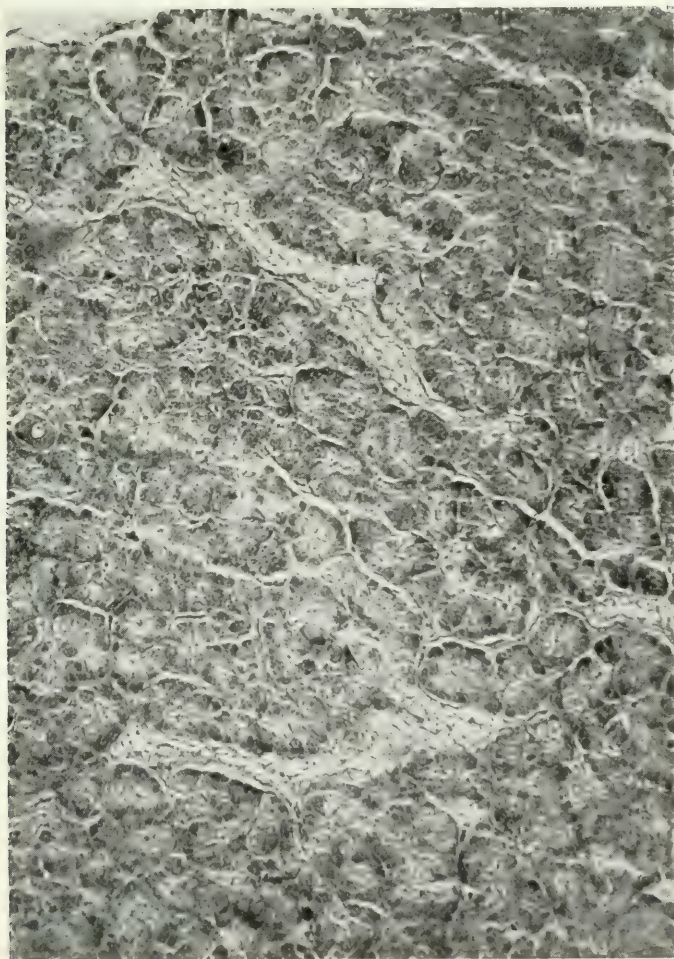


FIG. 18.

× 250.

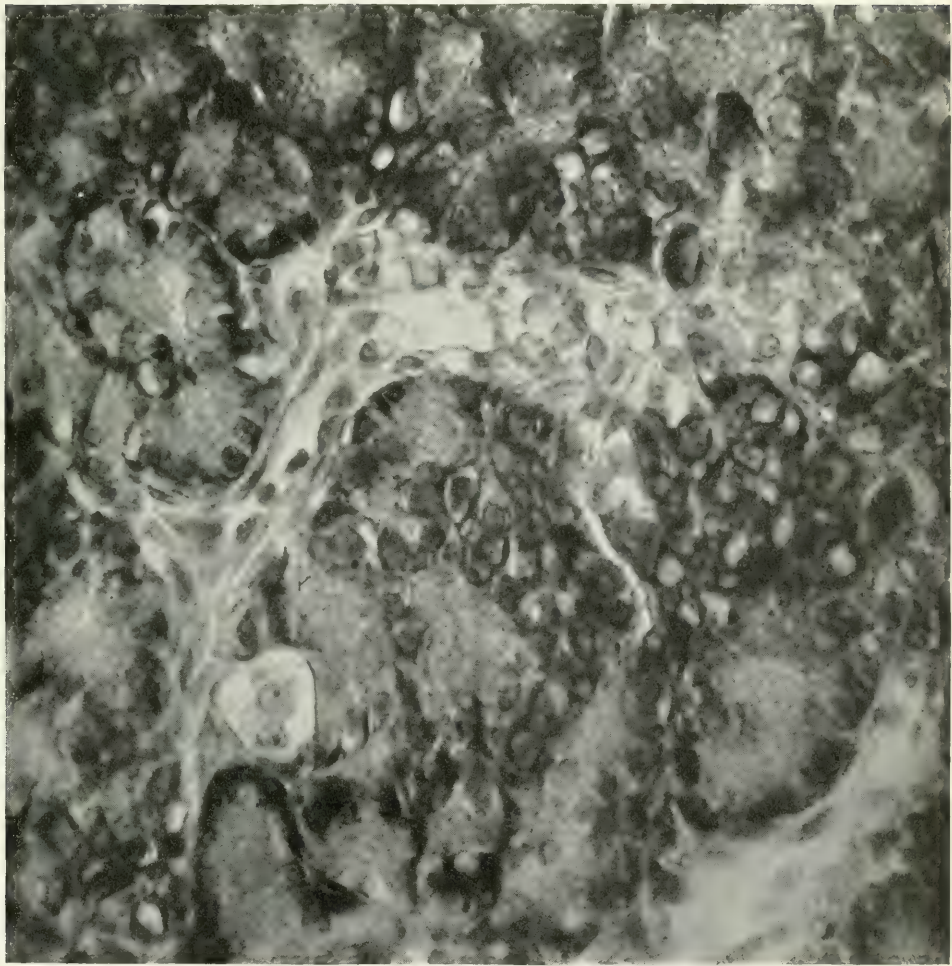


FIG. 19.

× 700.

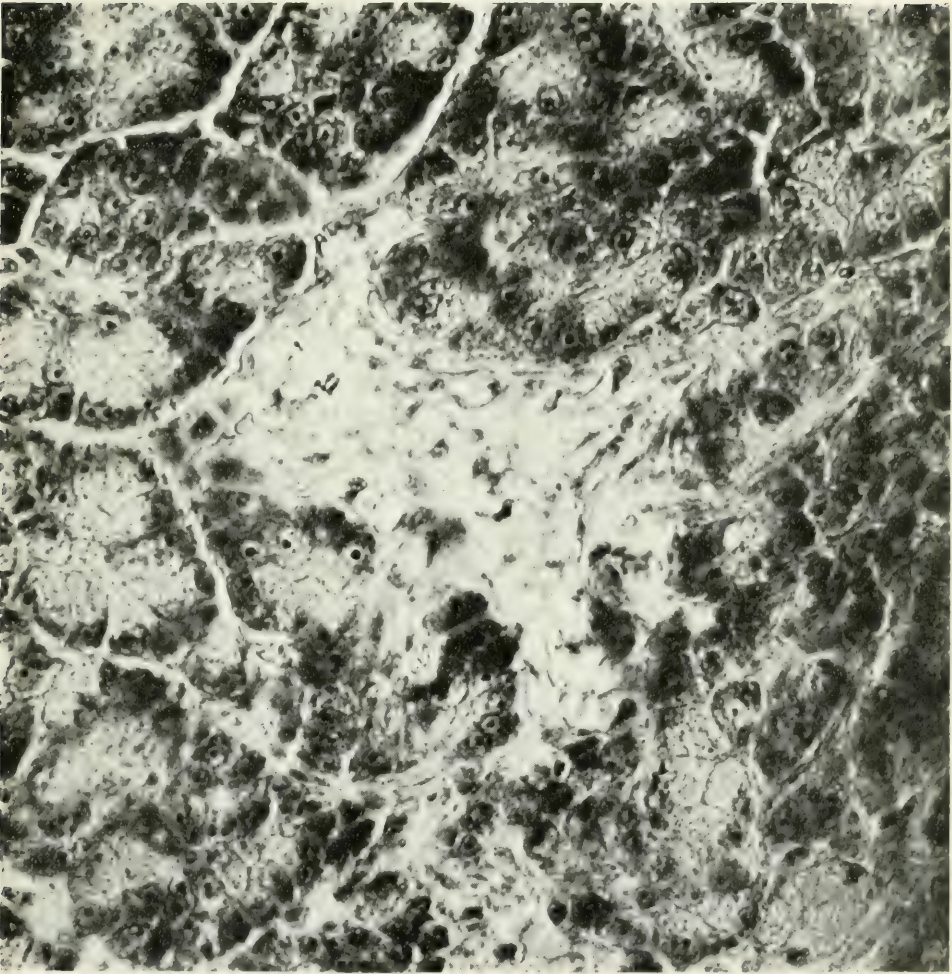


FIG. 20.

× 700.

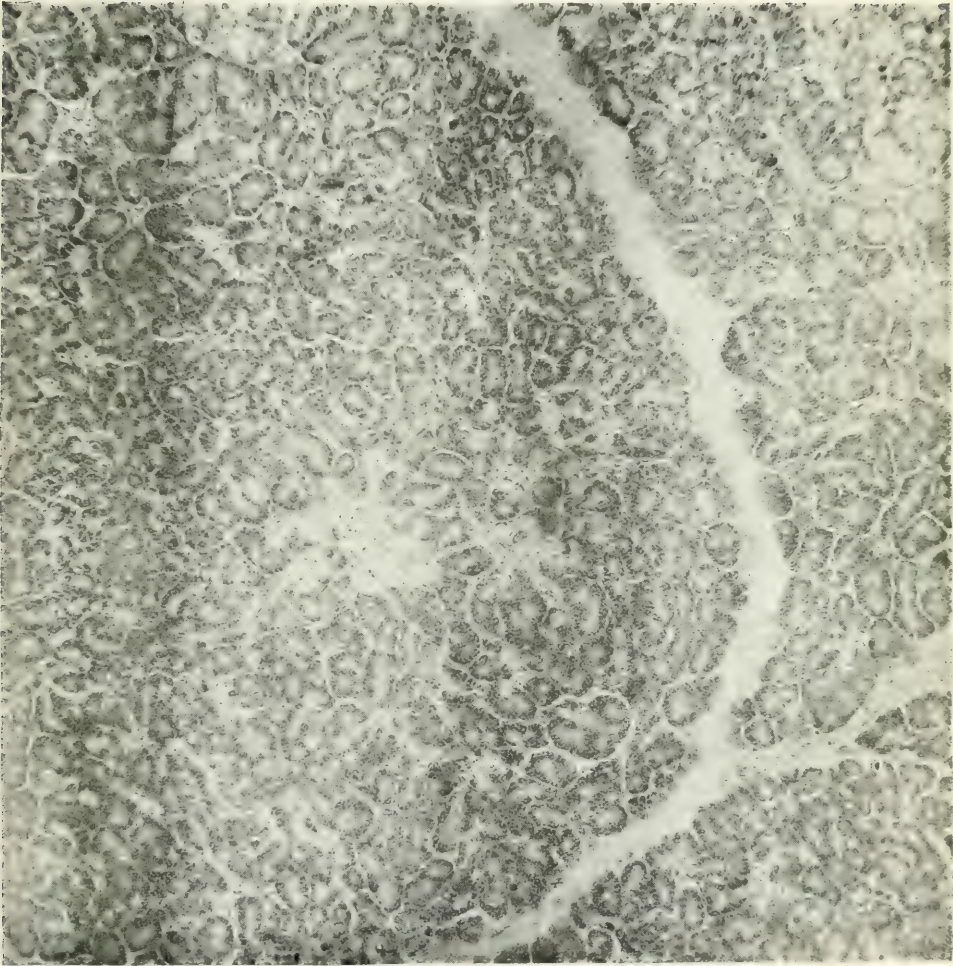


FIG. 21.

of severe experimental diabetes. The significance of this phenomenon is hypothetical, but it may represent the exhaustion of a proliferative rather than of an endocrine activity.

5. The existence of "total" diabetes from the standpoint of carbohydrate metabolism after the complete exhaustion or disappearance of the beta cells, though the alpha cells survive and retain full granulation, indicates that the beta cells alone furnish the internal secretion which is concerned in the sugar economy. The differences that still exist between such an animal and a totally depancreatized animal furnish evidence, first, that the profound cachexia following total pancreatectomy is not due solely to the failure of carbohydrate metabolism or the hyperglycemia or glycosuria resulting from this failure; and second, that the alpha, duct, acinar or other cells of the pancreas furnish an unknown internal secretion which is somehow important for the welfare of the organism.

6. The demonstration of the nature of the hydropic change is important for the following reasons:

(a) Its presence affords a positive microscopic diagnosis of active diabetes.

(b) It completes the proof of the island theory of diabetes.

(c) It adds to the evidence of the essential identity of experimental and clinical diabetes.

(d) It explains the permanent lowering of assimilation in diabetes consequent upon excessive diets.

(e) From a broader physiological standpoint, it offers the only proved example of anatomic breakdown of cells due to over-stimulation of an internal secretory function.

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EXPERIMENTAL STUDIES IN DIABETES

SERIES III. THE PATHOLOGY OF DIABETES

2. GRANULE STAINS OF THE ISLANDS OF LANGERHANS OF THE DIABETIC AND NON-DIABETIC PANCREAS.

By WALTER B. MARTIN, B.S., M.D.

*From the Hospital of the Rockefeller Institute for Medical Research,
New York.*

The existence of two kinds of cells in the pancreatic islands was recognized by Schulze¹, Diamare², and Dewitt³, but these were most conclusively demonstrated and studied by means of a special staining method by Lane⁴ in 1907. Bensley⁵ in 1911 made the most complete study of the cytology of the pancreas, finding in the islands not only the alpha and beta cells described by Lane but also a third type (possible less differentiated) designated as gamma cells. By the specific granulation, mitochondria and other characters the island cells, whether in the islands or scattered elsewhere, could be positively distinguished from all other pancreatic cells, such as acinar, duct and centroacinar cells. The alpha and beta cells were asserted to be independent types and not derived from or transformable into one another.

Homans⁶ confirmed the different staining reactions of the alpha and beta granules with the Lane-Bensley dyes, and also demonstrated a functional separation between the two types by discovering that only the beta cells suffer loss of granules and degeneration in experimental diabetes, while the alpha cells persist with the usual or even heavier granulation. He later was able to demonstrate a similar vacuolation of the beta cells in a case of human diabetes.

The present studies were carried out under the direction of Dr. Frederick M. Allen on normal tissues from the dog, cat, rat, rabbit, pig, guinea-pig, monkey and man, also on the organs of all of these species except man after partial pan-

createctomy, and on six cases of human diabetes. The tissue was treated according to the method of Bensley, but using a modified neutral stain as suggested by the writer.⁷

The purpose of this investigation may be stated briefly as follows:

First: To confirm the observations of previous contributors as to the staining characteristics of the alpha and beta cells, and to extend their investigation by applying the granule stain to the tissues of animals not yet studied by this method.

Second: To study the pathological changes in the islands of partially depancreatized animals under varied conditions of diet with the hope of extending our knowledge of the relationship of the secretions of the island cells to carbohydrate metabolism.

Third: The principal purpose was the application of the granule stain to human diabetic material to determine if anything could be added to our knowledge of diabetic pathology that would aid in the microscopic diagnosis of diabetes.

TECHNIQUE

A number of different fixatives were used, namely, Bensley's osmic bichrome acetic mixture, alcohol chrome sublimate, aqueous chrome sublimate, form-alcohol chrome sublimate, and Zenker's fluid containing acetic acid varying from one to three per cent. Of these the three given below were found the most valuable.

Fixatives. — (a) Aqueous chrome sublimate.

Mercuric chloride	5 gm.
Potassium bichromate	2.5 "
Distilled water to.....	100 cc.

The tissue was fixed in this solution for from four to twenty-four hours, washed in running water for twenty-four hours, passed through graded alcohols to absolute alcohol. A little iodine was added to the 70% alcohol in the graded series to extract the excess of bichloride. From absolute alcohol the tissue was placed in a solution of equal parts of oil of bergamot and absolute alcohol, remaining three or four hours, transferred to pure oil of bergamot and embedded in paraffin.

(b) Zenker's fluid (modified).

Mercuric chloride	5 gm.
Potassium bichromate	2.5 "
Glacial acetic acid	2 cc.
Distilled water to	100 "

The tissue was fixed in this solution twelve to twenty-four hours. The preparation of the tissue after leaving the fixative was the same as given above for the aqueous chrome sublimate.

(c) Alcohol chrome sublimate.

Made up of equal parts of saturated 95% alcohol solution of mercuric chloride and 2.5% water solution of potassium bichromate.

The tissue was fixed in this solution for two to four hours. The subsequent treatment was the same as given above for the other fixatives.

Stains.—(a) Neutral ethyl violet azo-fuchsin.

Basic ethyl violet combines with the acid azo-fuchsin in the proportion of two to one. Aqueous solutions of both dyes were prepared and the acid stain was added to the basic substance in the above proportion. The precipitated neutral dye was filtered, washed with distilled water and allowed to dry in the air. A stock solution of a known strength was made up in absolute alcohol. Staining solutions in 20% alcohol were prepared from the stock solution. One milligram of the dye to 100 cc. of 20% alcohol gives an effective staining solution.

The tissue was stained in this solution for twenty-four hours, washed in acetone to get rid of the excess dye, and then differentiated under the microscope with acetone until the purple zymogen granules stood out sharply against a pink background. The excess of acetone was blotted off and the section passed through toluol and mounted in balsam.

Tissues fixed in Zenker's or alcohol chrome sublimate and stained with neutral azo-fuchsin present a beautiful picture. On a pink background the zymogen stands out as dense purple granules. The nuclei of the cells stain fairly well, the chromatin material taking the acid fraction of the dye. The islands can be clearly differentiated; the granules of the alpha cells stain a deep violet while those of the beta cells are red. Differentiation of the alpha and beta cells from each other and from the surrounding acinar tissue is sharp and clear-cut.

(b) Neutral ethyl violet — Orange G.

Ethyl violet and orange G react in the proportion of two to one, resulting in a neutral dye. Preparation of the neutral substance and of the staining solution is exactly the same as given above for the azo-fuchsin except that a concentration of 2 mgm. per 100 cc. of 20% alcohol is required for the staining solution.

Sections stained with this dye show much the same picture as neutral gentian except the stain is much more intense and the differentiation is sharper. On a yellow background the zymogen appears as brilliant purple granules. The nuclei stain blue. Tissue fixed in the aqueous chrome sublimate shows the beta cells crowded with blue or violet granules, while the alpha cells are stained a diffuse yellow. More detailed description of these stains and their method of preparation has been given in an earlier paper.⁷

Preparation of tissue. — Wherever possible tissue should be taken absolutely fresh, cut with a sharp knife into pieces not more than one to two millimeters thick and placed immediately in the fixative. Material taken more than an hour after death is usually of little value. It has been found advantageous to have the fixative cold. The tissue is thus chilled immediately and the digestive action of the pancreatic ferments checked. As the penetrative power of these fixatives is poor, it is better to take material from the interior of the gland so as to insure the inclusion of island tissue in the portion well fixed. The necessity of obtaining the tissue fresh constitutes one of the principal objections to the use of the granule stain. All of our efforts are eventually directed to the study of human pathology, and it is obviously impossible in many cases to obtain human material within an hour after death.

In order properly to differentiate the alpha and beta cells, thin preparations are necessary. Sections must not be more than three microns in thickness; the appearance of the islands in thicker sections is often deceptive, as part of an alpha cell may overlie a beta cell and suggest the presence of both types of granules in a single cell. One important consideration is to use a stain that is sufficiently intense to allow for prolonged differentiation. Sections insufficiently stained fade out rapidly all over under the differentiating agents.

Study of the normal tissue of the animals enumerated above serves to confirm the observations of Bensley⁵ and Lane⁴ on the guinea-pig and Homans⁶ on the dog and cat. While the islands of various species differ somewhat in shape, size, vascularity and minor details of structure, it is evident that they all are composed of at least two types of cells containing granules that stain in a characteristic way; namely, the alpha cells are larger and much fewer in number, eccentrically placed, with an oval more vesicular nucleus, and when fixed in Zenker's fluid or alcohol chrome sublimate show numerous fine granules that take the basic dye; the beta cells, composing by far the greater portion of the island, are smaller, closely packed in rows along the blood capillaries, with a nucleus that is denser and more nearly round, and filled with granules that stain with the acid fraction of the neutral dye in tissue fixed in Zenker's fluid or alcohol chrome sublimate. Material treated with aqueous chrome sublimate shows the reverse picture, the beta granules being stained blue and the alpha granules red.

Occasional islands were found composed only of beta cells. As serial sections were not made this may have been due to the accidental relationship of the particular segment studied.

No effort was made during this investigation to study the third type of cell in the island, the so-called gamma cell of Bensley. The question of the origin of the island cells was also not covered. It may be stated, however, in confirmation of Bensley's suggestion of the origin of the alpha cells from the ducts, that from time to time isolated cells containing the characteristic alpha granules were found along the small ducts. In certain places island cells were seen that appeared to contain both types of granules. This picture might be produced by a thin section of one cell overlying another cell, especially as in the normal tissue cell borders are very indistinct. These observations were certainly not conclusive enough to justify opposition to the view of Lane and Bensley that the two types of cells are independent and distinct.

The evidence is convincing that the islands elaborate an internal secretion. The anatomical independence of the islands, the presence of characteristic granules in the cells, the absence of channels of communication through which an external secretion could flow, the vascular character of the islands and

the arrangement of the cells along the capillaries, the development of diabetes mellitus in experimental animals after extirpation of a sufficient portion of the pancreas, failure of the condition to develop when the parenchyma alone is destroyed and the islands left more or less intact, and the occurrence of specific changes in the islands with diabetes, make this conclusion inevitable. It is this fact that emphasizes the necessity of studying the minute structure of the islands and lends importance to the special staining methods that clearly demonstrate the granular contents of island cells.

The specific stains are valuable for two reasons: First, they enable one positively to identify island tissue wherever found. With routine stains this has not been an altogether simple matter, as evidenced by the long controversy waged over the question of whether or not the islands are independent structures or merely changed or modified acinar tissue. Following duct ligation with consequent extensive fibrosis of the pancreas, and after exhaustion of the acinar cells by prolonged stimulation, the appearance of the tissue is so changed that identification of the insular elements may become a difficult problem. Second, they show the uniform occurrence in all species thus far studied of two distinct types of cells. This suggests the possibility that two distinct internal secretions may be elaborated in the islands and opens up an interesting field for further investigation.

Observations on material from animals rendered diabetic or nearly diabetic by partial pancreatectomy served to confirm the findings of Homans in his investigations on dogs and cats. The outstanding change in the islands in these experimental animals was the so-called hydropic degeneration affecting the beta cells. There is first a thinning out and finally a complete disappearance of the beta granules; the cell body becomes swollen and more sharply outlined. At this stage there is nothing to indicate cell degeneration. The nucleus is normal in appearance and the cell outline is preserved, the picture being that of an active but exhausted cell. Later degenerative changes take place, the nucleus becomes shrunken and pyknotic, the protoplasm consists of irregular shreds inside of the hollow outline of the cell. Frequently the continuity of cell outline is broken and considerable areas are seen containing a mass of cell debris. No change similar to the hydropic

degeneration of the beta cells is observed in the alpha cells. At no time was a diminution of the alpha granules noticed; in fact the alpha cells often stained more deeply and were apparently more closely packed with granules. Whether this appearance was due to an actual increase in the granules or merely to the crowding together of the alpha cells by the swollen beta cells, it is not possible to state. In the end stages of experimental diabetes the beta cells may be altogether lost and the persisting islands made up of a small compact group of alpha cells crowded with granules. The degeneration of the beta cells, presumably under the strain of over-stimulation, with the failure of the alpha cells to respond to the same stimulation, strongly confirms the opinion of Lane and Bensley as to the independence of the two cell types.

As the principal purpose of this investigation was to determine the value of the granule stain in the study of diabetic pathology, it may be well to consider the merits of these special stains as compared to the older routine method. It was conceivable that abnormalities of granulation might be detected where the ordinary stains gave a normal appearance, also that apparently normal islands in some cases of human diabetes might be found to be made up chiefly or wholly of alpha cells. Studies were therefore made of the pancreas from seventy-nine specimens from dogs, thirty-eight from cats, and several from other species at various stages after partial pancreatectomy. The specimens were often taken from the same animal at successive operations which produced various degrees of lowered tolerance culminating in frank diabetes. The tissue taken at the first operation served as a control. The material was obtained from different parts of the tissue removed and a number of slides prepared from each block so that all parts of the pancreas were adequately studied. Especial attention was given to material from three groups of cases. First, animals which were not diabetic but were so near the verge that removal of a very small additional fragment of material would suffice to bring on diabetes. Second, non-diabetic animals on which feeding experiments with glucose were carried out. Third, diabetic animals in which an effort was made to control or modify the diabetes by diet. Results confirmed those obtained with the ordinary stains. The granule stains are more difficult in their application and

more uncertain in their results and they add little of importance for the recognition of either clinical or experimental diabetes.

We may consider that there are four stages of alteration in the islands of diabetic animals. First, the stage in which the beta cells appear swollen, more sharply defined, with a thinning out of their granular contents. Second, the stage of vacuolation of the beta cells. The cells are completely emptied of granules and show a clear protoplasm with a well preserved nucleus and cell outline. Third, the stage of degeneration of the beta cells, marked by shrinkage of the nucleus and breaking down of the cell body. Fourth, the disappearance of the beta cells, leaving islands made up of alpha cells alone. In the detection of the first three types of changes noted, the granule stains present no great advantage over the routine procedure. When tissue is taken absolutely fresh, as the special stains require, fixed and stained well by the routine methods, hydropic changes in any one of the three stages are perceptible if present. The fourth stage, when the islands are made up of alpha cells alone, has only occasionally been observed in experimental animals, never in a case of diabetes in man.

The results obtained from the application of the special methods of staining to human diabetic material have not been conclusive. While these methods by clearly revealing all tissue of island character have confirmed the quantitative deficit of island tissue in certain cases of human diabetes, in other cases, however, where the routine stains show large numbers of normal appearing islands with or without hydropic changes in a few, the special stains may also reveal the usual proportion of alpha and beta cells with apparently normal granule contents. We therefore still face the necessity of assuming some functional alteration as the basis of diabetes in man. The same conclusion seems to have been reached by Homans from unpublished observations.

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NOTES ON THE FIGURES.

Colored stereopticon slides were successfully made from some of these sections by Mr. Louis C. Schmidt, to whom thanks are due for assistance and advice with the illustrations. When it appeared impracticable to use any method of direct reproduction for publication, drawings were made for the purpose by Miss E. C. Babb. Oil immersion fields under the granule stains are accurately represented, each figure showing an island of Langerhans and a border of surrounding acinar tissue.

Fig. 1. — Pancreas of normal dog, Zenker fixation, neutral ethyl violet-orange G stain. The acini contain variable quantities of zymogen, appearing as masses of purplish blue granules. With accurate focussing upon the original preparation, these granules are recognized as very large and distinct, like buckshot. The island, demarcated by dilated capillaries, consists as usual chiefly of beta cells, which take the yellowish background stain and are poorly delimited from one to another by any visible membranes. Several alpha cells are present, two of them being indicated by the pointers. They are distinguished by the very fine blue granules which fill them.

Fig. 2. — Pancreas of diabetic dog with hyperglycemia for several weeks but no glycosuria. Zenker fixation, neutral ethyl violet azo-fuchsin stain. The acini contain relatively little zymogen, but indistinct masses of it are seen in some cells. Here also focussing in the original preparation reveals these masses as composed of large, purple, buckshot granules. The contracted capillaries of the island are scarcely visible. Some of the beta cells of the island are moderately vacuolated but the others still show the normal content of pink-stained granules. Two of the alpha cells present are indicated by the pointers. They retain their characteristic blue-stained granulation.

Fig. 3. — Pancreas of dog with active diabetes. Zenker fixation, neutral ethyl violet azo-fuchsin stain. Zymogen is present in larger quantity in most of the acini, and appears as masses of large blue-stained granules. Vacuolation in the beta cells of the island is more advanced. The pointers show two alpha cells with undiminished granulation.

Fig. 4. — Pancreas of dog with more severe diabetes. Zenker fixation, neutral ethyl violet azo-fuchsin stain. The abundant zymogen in the acinar cells again appears as large blue masses. It will be observed that in this and the preceding slide the differentiation has been made in favor of the blue stain, so as to bring out the alpha cells as prominently as possible. One beta cell at the bottom of the figure is maximally vacuolated. Others show different stage of vacuolation and degeneration. A minority still retain normal granulation. Three alpha cells are indicated by the pointers. Their dense blue coloration may be only partly due to the slight overstaining with blue, and may partly represent a closer crowding of granules than in the normal.

Fig. 1.

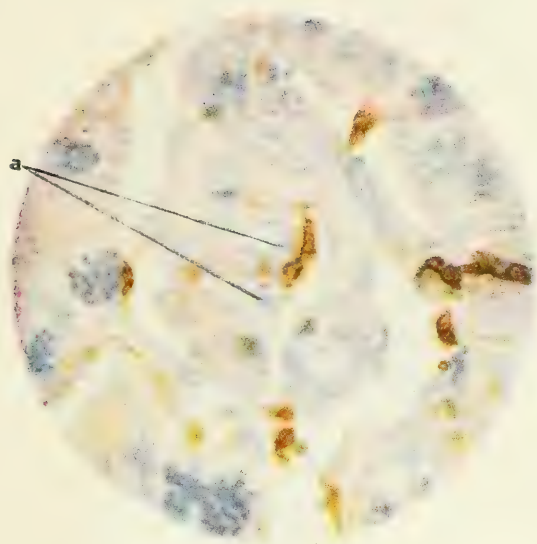


Fig. 2.

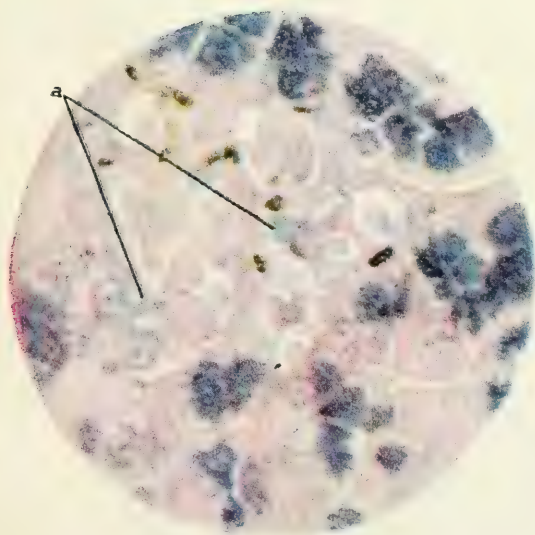
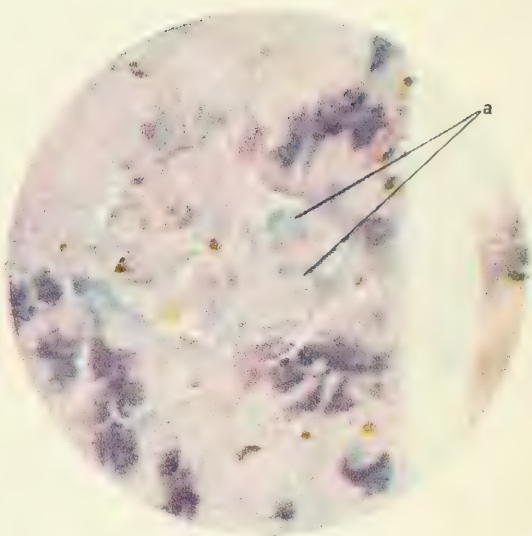


Fig. 3.

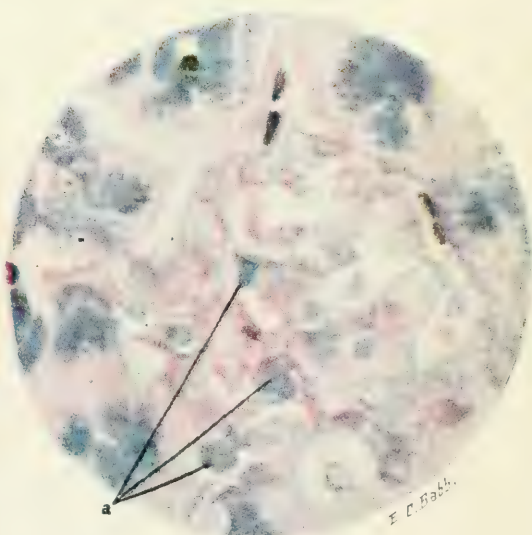


Fig. 4.

EXPERIMENTAL STUDIES IN DIABETES.

SERIES III. THE PATHOLOGY OF DIABETES

3. NERVOUS INFLUENCES IN THE ETIOLOGY OF EXPERIMENTAL DIABETES.

BY FREDERICK M. ALLEN.

*From the Hospital of the Rockefeller Institute for Medical Research,
New York.*

One of the principal theories of the origin of diabetes has been that of a nervous derangement of some kind. Experimentally, this view has received support from Claude Bernard's picture of the medulla and other forms of transitory nervous glycosuria, and clinically from the supposed neurotic character of diabetic patients, the observations of alleged "traumatic" diabetes coming on after injuries, the frequently reported increase of glycosuria with emotional disturbances, etc. Naunyn ranked the nervous system and the pancreas on an equality as the two positively established locations of the cause of diabetes. The present writer¹ inclined strongly to the nervous hypothesis on the basis of the evidence existing in 1913, but the recent advances in knowledge of the subject have cast much doubt on this view². The experimental nervous glycosurias are evidently not diabetes nor due to pancreatic disturbance. There is no proof of the causation of a single clinical case of diabetes by mental strain, emotion, shock, wounds or any of the formerly suspected influences, either in civil life or in the recent war. The growing evidence of the origin of diabetes in pancreatitis also contributes to rule out nervous disturbance as an etiologic possibility.

At the same time conservatism must be used in forming conclusions in a complex subject, and certain questions concerning the nervous hypothesis are important for investigation. Attention should be given to the broad general probability that all glandular (including endocrine) functions are to some

extent under nervous control, either of direct secretory or at least of vasomotor character. With regard to the primary origin of diabetes, when fibrosis is seen in the pancreas the first assumption is of an infectious or toxic cause; but it is commonly recognized that in the kidney, for example, both functional and anatomic abnormalities may result from a simple circulatory disorder, as in heart disease. The possible influence of some unknown vasomotor disturbance, such as suggested by some of the old sympathetic nervous hypotheses of diabetes, therefore remains to be investigated. Also, every anatomic explanation of diabetes still requires to be helped out by the assumption of functional deficiencies in the islands in certain cases. It is conceivable that such deficiencies lie in the nervous control, and that the local nerves or ganglia may sometimes suffer injury in an acute pancreatitis, or that in-born nervous peculiarities in some individuals or families may create a susceptibility to diabetes from injuries which are too slight to cause serious harm in normal persons. Furthermore, even if the nervous system should be found to have no part in the primary origin of diabetes, the possibility that it may at least have an influence for good or ill upon the course of an existing diabetes is strongly supported in clinical literature. The role of the nervous system in the production of hydropic degeneration of the islands is also an open question. An investigation was therefore undertaken of certain functional and anatomic influences.

I. EMOTIONAL INFLUENCES.

The total series afforded a large number of incidental observations of the influence of emotion. Dogs and cats sometimes come to the laboratory in a state of intense fear, which may be prolonged for a number of days on account of the strange surroundings. Partial pancreatectomy performed in this condition was not found to create any more than the usual degree of diabetic tendency. Also dogs with existing latent or active diabetes were subjected to various forms of pleasant or unpleasant excitement, with no apparent specific effect. Such dogs are naturally subject to somewhat greater emotional hyperglycemia than non-diabetic animals, but figures are not worth reporting because of individual variations, chiefly for

want of any measure of the degree of emotional disturbance. Such hyperglycemia very rarely reaches the point of glycosuria even in dogs with potentially severe diabetes under dietary control. The influence is generally greater in small nervous dogs than in large phlegmatic ones. One little dog, depancreatized not quite to the point of diabetes, showed traces of glycosuria whenever brought from the animal room to the laboratory, but all attempts to maintain this glycosuria or bring on a true diabetes failed. Numerous direct experiments were performed upon dogs depancreatized to such a point that the removal of a fraction of a gram of additional tissue would bring on diabetes, and also upon diabetic dogs with carefully tested tolerance on weighed diets, by keeping them in uncomfortably small cages, or in dark isolated rooms or under other conditions to produce worry; but though the most nervous animals were selected for this purpose, it was never possible to bring on diabetes or prolonged glycosuria in a non-diabetic dog or perceptibly lower the food assimilation of a diabetic one. Also rabies or the nervous form of distemper, though attended with convulsions or mania, never caused even a transitory glycosuria in partially depancreatized dogs, and the same was true of dumb rabies.

As the cat is particularly subject to emotional glycosuria and also becomes diabetic with removal of a smaller proportion of pancreatic tissue than the dog, it seemed to offer the most favorable material for experiments. A series of 12 cats were depancreatized just short of diabetes, or again to the point of mild diabetes, and were subjected to rage and fear by methods similar to those of Cannon³, namely either by tying on the back for several hours, or by placing the cat's cage in the center of the dog room, where it was the object of interest to the dogs in the cages on all sides. The results were disappointing, because the glycosuria and hyperglycemia were actually less than those frequently observed in normal cats. The chief difficulty was that by the time the cats had undergone partial pancreatectomy and their tolerance had been established they were too tame to react with any wild excitement, but the experiments afforded no hope of any production of diabetes by this means under any conditions.

Surgical operations upon animals which were diabetic or nearly diabetic have rarely been followed by glycosuria, and

this has always been very brief and has left no permanent influence upon the diabetes. Animals in various conditions from normal to diabetic have undergone shock in various incidental experiments, but when they survived there has been no aggravation of the diabetes, and when they died there have been no alterations in the pancreas. Such observations have been made after amputation of limbs, handling of viscera, removal of fatal amounts of liver or kidney tissue, also after hemorrhage and after total epinephrectomy. In particular, no vacuolation of the islands of Langerhans results from any of these procedures.

The only observation of a possible traumatic aggravation of diabetes was the following accidental one.

Cat B2-12.—Male; black and white; large strong adult; excellent nutrition; weight 3.8 kilos. Nov. 5, 1914, removal of pancreatic tissue weighing 9.7 gm. Remnant about main duct estimated at 2.6 gm. (1/4-1/5). Glycosuria ensued on a diet of meat and milk but tended to diminish, even with addition of glucose up to 30 gm.

Dec. 15, 0.3 gm. additional pancreatic tissue was removed. This was normal throughout, with abundant islands free from vacuolation. More or less glycosuria had been present every day for over 5 weeks, and the absence of hydropic changes therefore indicates a very mild or transitory diabetes. Such absence is unusual in animals but is familiar in mild human cases.

After this operation glycosuria could be produced by milk feeding but was absent on a diet of beef lung. The cat was kept in this condition of latent diabetes and was used for a series of feeding tests.

Aug. 4, 1915, with glycosuria absent on a regular diet of 500 gm. beef lung, the cat escaped from his cage and was badly injured in a fight with a bulldog. He was semi-conscious when rescued, but yet had received no extensive lacerations or apparently dangerous wounds. No glycosuria occurred at this time or during the two weeks following, while the cat was eating very little. But as soon as recovery had reached a point where the former diet was taken, the following urine record was obtained:

Date—1915	Volume cc.	Glucose, per cent
Aug. 18.....	158	1.11
" 19.....	60	1.96
" 20.....	249	0.34
" 21.....	160	1.20
" 22.....	280	2.60
" 23.....	193	0.34
" 24.....	200	0.63
" 25.....	190	0.32
" 26.....	250	0.73
" 27.....	170	1.00
" 28.....	189	0.37

Fasting was then imposed, and the glycosuria fell to traces in 24 hours and ceased withing 48 hours. Meat diet was then begun with 100 gm. of beef lung, and increased gradually so that 500 gm. of either lung or heart could soon be eaten without return of glycosuria.

As it has been claimed that in some human traumatic cases the onset of glycosuria has been delayed for some time after the accident, it seems possible that the glycosuria in this cat was a result of the injury. In any event it represented not a production of diabetes but merely a lowering of tolerance in an animal already diabetic; and this lowering was transitory and the original tolerance was fully recovered. The diabetes might have proved permanent had fasting not been used to check it, because the injury of over-feeding would have been superimposed upon the traumatic disturbance. By temporary relief from the over-feeding it was possible to show that the lowering of tolerance was actually temporary and therefore probably associated with the trauma.

II. PIQURE

Claude Bernard was probably correct in interpreting his puncture of the medulla as an irritative nervous lesion giving rise to hyperglycemia and glycosuria by over-production of sugar due to a rapid discharge of liver glycogen. He furthermore regarded the condition as temporary diabetes; but true diabetes is now known to be an impairment of sugar utilization; also it is scarcely conceivable that a nervous disturbance could produce diabetes more quickly than total pancreatectomy, or that this diabetes should cease as soon as most of the liver glycogen is discharged and should remain absent when the existing store of glycogen is small. Nevertheless it is certain that the piqure sends some kind of strong nervous impulse to the abdominal viscera, which in addition to the effect upon the liver may cause the adrenals to discharge epinephrin and usually acts on the kidneys to cause polyuria, and which therefore may exert some influence upon the pancreas.

The writer formerly applied the Bernard procedure to partially depancreatized dogs, but the results were transitory except in one animal, namely dog No. 63⁴. In this experiment the pancreas remnant was between $1/4$ and $1/5$ of the pan-

creas, and the dog remained free from diabetes from the time of this operation on June 13 until July 17. Then a Bernard puncture was performed, with the result of heavy glycosuria which continued to death on July 23. The condition was the more remarkable because of the simultaneous onset of marked acetonuria. More recent attempts to duplicate this result were on the whole unsatisfactory, with the following single exception.

Dog B2-41. — Brindle female mongrel, age 5 years, in medium nutrition, weighing 14.7 kilos. Feb. 18, 1918, removal of both processes of pancreas, weighing 19.2 gm., leaving the body of the gland estimated at 8.1 gm. (1/3-1/4). Glycosuria remained absent on bread and soup diet. Beginning March 23, 200 gm. glucose was added to the diet, increased on March 26 to 300 gm. and on March 30 to 400 gm., without glycosuria. This diet with 400 gm. glucose continued through April 12, but on April 13 nothing but meat was fed.

April 14, without food, the skull was trephined under ether and two punctures of the medulla made by Bernard's method, by stabbing through the cerebellum with a narrow "chisel" after Bernard's original pattern. On recovery from the anesthetic the dog was profusely salivated and partially paralyzed, with deviation of position and movement to the right. At the same time the animal quickly regained good spirits, and 50 gm. glucose in 300 cc. solution given by stomach tube 2 hours after the operation was retained without apparent nausea.

Glycosuria was heavy and continuous. April 15, the dog could eat only a few small pieces of bread and meat on account of jaw clonus, but retained another 50 gm. glucose given by stomach tube.

On the following days the spirits and general strength remained good, and the dog became able to walk in drunken fashion. Appetite was present, but only small quantities of bread and meat could be taken with assistance on account of the trouble with the jaw muscles. Daily doses of 100 gm. glucose given by stomach tube were retained without nausea or diarrhea until April 19, after which there was more or less vomiting because the glucose was increased to 200 gm. daily. Glycosuria continued heavy (in the neighborhood of 4%) and the general condition seemed to be actually improving, until the dog was found dead on the morning of April 24.

Autopsy showed both punctures accurately placed, one behind the other in the sugar area of the floor of the fourth ventricle. There was pneumonia of both lungs, presumably due to aspiration of vomited glucose solution. The pancreas remnant, weighing 8.25 gm., was normal in both gross and microscopic appearance. Islands were numerous though mostly small, but the question of vacuolation could not be decided because of postmortem change.

This case is not as good as that of dog No. 63, but tends to confirm that result. All other attempts in this series failed

for the same reason as before; namely, the dogs either died from the brain injury or associated complications, or with slighter injury they exhibited only a transitory glycosuria and regained the full tolerance which they possessed before the pique. Some attempts were also made to set up a more chronic irritation by sterile injections of a suspension of kieselguhr into this area of the medulla, but these likewise failed. The total results are not yet decisive, but it is hoped to repeat the attempts hereafter with a more efficient method of stimulation.

III. ENERVATION AND GRAFT EXPERIMENTS

These experiments pertained to two questions: first, whether interference with the nerve supply to the pancreas remnant has any influence upon the production of diabetes; second, whether the hydropic degeneration of the islands is governed by nervous or humoral agencies. Two elements in the local innervation of the pancreas also require attention; namely the extrinsic supply of fibres derived from the vagus and sympathetic system, and the intrinsic apparatus in the form of the numerous intrapancreatic ganglia and the fibers derived from them. If all nerves entering the pancreas are divided, the possibility is still open that some control may be exercised by the local ganglia.

Two methods seemed to offer possibilities for the removal of these ganglia. One may be called an attempt at differential asphyxia. The plan of clamping the vessels, as described in paper 6, was devised not merely to set up inflammation, but also with some expectation that the intrapancreatic nerve cells might be more sensitive to asphyxia than the epithelium, so that they might be killed or seriously damaged by lack of blood for periods which the parenchymal cells would readily survive. This anticipation proved erroneous, and one of the surprising observations was the fact that the ganglia persisted apparently uninjured after asphyxia for as long as two hours. The other hope, in connection with graft experiments, was based on the question whether nerve cells can be successfully transplanted along with the tissue containing them. The writer knows of no experiments covering this point in adult mammals, but something analogous seemed to be contained in reports that in adrenal grafts the cortical cells ordinarily survive but the

chromaffine cells, which are of sympathetic origin, die out. In pancreatic grafts, with section of the extrinsic nerves and with the necessity of adjustment to a new blood supply, there seemed to be a chance that the ganglia might degenerate. The contrary proved to be the case, for no signs of injury were seen in the ganglia and their abundance in successful grafts sufficed to exclude any important numerical reduction.

The experimental possibilities were thus limited to the extrinsic nerves, which might be either stimulated or sectioned. The earlier literature of attempts to produce diabetes by peripheral nervous irritation was previously reviewed⁵, and was negative apart from transitory glycosuria. The writer formerly⁶ obtained no increase of diabetic tendencies by breaking of nerves or by superficial lacerations of the pancreas remnant and its neighborhood. Homans⁷ electrically stimulated the splanchnic nerves of normal and partially depancreatized animals for 7 to 10 hours without producing vacuolation in the islands of Langerhans. Though these are the best experiments, the time was probably too short for the production of hydropic changes⁸, and the question of nervous irritation is still not entirely closed.

Complete separation of the pancreas from its usual extrinsic nerve supply can be accomplished by removing all of the organ except a graft placed in the spleen or subcutaneous tissue, and later cutting the pedicle of this graft. Though new nerves grow into the pancreas from the new environment, they cannot possibly be supposed to carry impulse to or from any centers normally regulating the pancreatic activity. Such experiments by a series of authors have not given rise to diabetes⁹. Likewise section of all discoverable nerves of the pancreas remnant left *in situ* has in the present writer's experience created no increased or decreased tendency to diabetes¹⁰. These experiments leave certain points open. With the pancreas remnant left *in situ*, there is the possibility that some nerve filaments remain unsevered, and also that fibers from the old trunks may grow back, so that hydropic changes in such a remnant might still be due to nervous influences. In the graft experiments, generally so much pancreatic tissue was transplanted that an increased tendency to diabetes from cutting the pedicle might be missed; also cachexia due to lack of pancreatic juice would interfere with the development of

diabetes and with accurate tests of the food tolerance; and no observations of hydropic changes were made by these authors. A series of graft experiments were therefore performed, partly as simple repetition and partly to cover new points.

Dog B2-62.—Female; mongrel; brindle; age 5 years; good condition; weight 9 kilos. May 22, 1914, removal of pancreatic tissue weighing 14.7 gm. The portion left consisted of the uncinate process, estimated at 5.8 gm., with its duct stripped bare for about 1 cm. The dog remained in good condition, and a series of glucose tests subcutaneously and by stomach showed a tolerance of 8 gm. per kilo, traces of glycosuria occurring with 9 gm. per kilo.

Nov. 24, when the weight was 10.2 kilos, the pancreas remnant was found normal in appearance, and after removal of 0.2 gm. of its tissue for specimens, it was completely imbedded in the spleen, leaving intact its pedicle of vessels and nerves at one end and its duct at the other, so as to create no interference with either the circulation of blood or the drainage of pancreatic juice.

Dec. 17, the weight being still 10.2 kilos, the vessels and nerves and all other connections of the pancreas remnant were severed except the isolated duct, which was stripped as bare of all nerves or other tissue as possible. The dog continued to thrive, and on March 30, 1920, at a weight of 12.4 kilos, tolerated 81 gm. of glucose subcutaneously without glycosuria (9 gm. per kilo on the former weight of 9 kilos). Likewise on April 8, 72 gm. of glucose by stomach tube caused no glycosuria.

April 14, when the weight was 11.6 kilos, the duct and all other extra-splenic connections of the pancreas were divided, and 0.1 gm. of tissue taken as a specimen. The dog then lost weight through indigestion, down to a final weight of 9.3 kilos, but otherwise seemed fairly well till unexpectedly found dead on the morning of April 29.

The autopsy indicated that one end of the pancreas remnant, where the splenic tissue had been separated from it for purposes of inspection, had undergone necrosis, or else a collection of pancreatic juice had become infected, resulting first in a walled-off abscess, the bursting of which had caused fatal peritonitis. The remaining pancreatic tissue was firmly imbedded in the spleen, appearing somewhat whiter than usual but otherwise normal and not sclerotic. Its weight was 9.35 gm., which seemed to represent true hypertrophy. Microscopically, the tissue from the operations of Nov. 24 and April 14 and from the autopsy was essentially normal, a slight fibrosis particularly at the periphery being the only change in the graft. A supply of vessels and nerves from the spleen into the surface of the graft was readily demonstrable, and there were no other outside connections of the graft.

The experiment proved that the glucose tolerance is not lowered when a pancreas remnant in the spleen is separated from all its original connections other than its duct, also that

the division of the duct does not then give rise to either diabetes or vacuolation of islands.

Dog B2-92.—Male; mongrel, black and tan; medium nutrition; weight 13.4 kilos. April 16, 1915, removal of splenic process and body of pancreas to near main duct, weighing 14.9 gm., leaving the remainder of the body and the uncinate process estimated at nearly the same weight. The duodenum was then brought close against the abdominal wall and the pancreas remnant imbedded in the wall, shut off from the abdominal cavity by closure of the peritoneum except for a small opening at each end, one for the duct and accompanying vessels, and the other for the inferior pancreaticoduodenal vessels and nerves.

The digestion was poor and by May 27 the weight had fallen to 9.7 kilos. Operation on that day showed that the pancreatic duct had become obliterated through kinking or stretching. The vessels and fibrous tissue in this region were ligated and divided, leaving the pancreaticoduodenal pedicle undisturbed.

The dog remained lively and managed to maintain a weight of 9.5 to 9.7 kilos by eating large quantities of bread and soup with a smaller allowance of meat and fat. Blood tests showed hyperglycemia, and on July 20 the first glycosuria appeared (1.2% sugar in 439 cc. urine). The plasma sugar on this day started at the normal level of 0.098%, rose to a maximum of 0.224% during digestion, and fell to 0.104% 8 hours after feeding. The glycosuria recurred daily till stopped by a fast-day on July 23.

At this time a small sinus at one end of the operative scar was still discharging clear pancreatic juice. On July 23 an incision was made over the other end of the pancreas remnant, 0.15 gm. of tissue was removed as a specimen, the pedicle of pancreaticoduodenal vessels and nerves was divided between ligatures, and the inner surface of the abdomen was explored to make sure that there was no structure of any kind passing from inside the abdomen to the pancreas graft.

Glycosuria did not follow this operation, and remained absent on a diet of beef lung, lard, raw pancreas and bone-meal, though increasing hyperglycemia was found. Aug. 9, 0.17% of sugar appeared in 680 cc. urine on this carbohydrate-free diet, and increased on the following days. The weight remained between 9.5 and 9.8 kilos till Aug. 28, then began to fall rapidly. The glycosuria at this time was over 3% in over a liter of urine daily. The feces weighed several hundred grams each day, and analyses showed very poor utilization of protein and fat. Sept. 13 the dog was killed when moribund from weakness at a weight of 8.5 kilos. The autopsy was negative except for the pancreas remnant, which had atrophied to a weight of 1.2 gm.

Microscopically, the tissue from the operation of July 23 showed degenerating parenchyma engulfed by fibrous tissue. The acini displayed the usual gradations from fully normal zymogen content to extreme emptiness and involution. Islands were scarce and hard to distinguish amid the confusion, and attempts to differentiate them by

means of Bensley stains failed. Their cells were free from any vacuolation.

The tissue from the autopsy was in the last stages of atrophy and fibrosis. Occasional acini still maintained their normal appearance and zymogen content, but the majority were going to pieces amid scar tissue. Over wide areas ducts of various sizes were the only remains of parenchyma. There was no selective sparing of islands. Even in the best preserved areas they were broken up by invading fibrous tissue, and a distinction between island cells and involuted acini and perhaps also duct cells which resembled them in size and form would have been impossible except for the hydropic changes. The unmistakable, wide, clear vacuolation of the beta cells picked them out better than a specific stain, and illustrated the independent occurrence of this change regardless of any other pathological processes. (*See also paper 6, Figures 2 and 3.*)

The diabetes was evidently of the Sandmeyer type, and was sufficiently explained by the atrophy of the pancreas remnant without the assumption of a nervous factor. The experiment proved that extreme hydropic changes of island cells can occur in a pancreas graft separated from all intra-abdominal connections.

Dog C3-02.—Male; bull terrier; white; age 4 years; good condition; weight 15.4 kilos. May 19, 1915, removal of splenic process and body of pancreas weighing 25 gm., leaving uncinat process estimated at 7 gm. (1/4-1/5). The right Rectus muscle was split and the pancreas was inserted in it so as to be surrounded chiefly by muscle tissue. The pancreatic duct, stripped bare for about 1 cm., remained as a pedicle at one end of the remnant, while two other pedicles near the other end were composed of vessels and nerves. The dog continued in apparently normal health on bread and soup diet, till glycosuria appeared on June 17 and continued to June 20. It then ceased on changing the diet to beef lung, returned heavily with resumption of bread feeding on July 12, and ceased promptly with lung diet on July 13.

July 23, when the weight was 12.7 kilos, opening the abdomen revealed only a fibrous cord in place of the principal pedicle of vessels and nerves, probably because of stretching. A small button of duodenum bearing the papilla of the pancreatic duct was excised and sutured into an opening in the skin. The duodenum was repaired and dropped back into the abdomen, and all intraabdominal connections of the pancreatic graft were divided.

No glycosuria followed the operation. The weight was kept nearly constant on a diet of lung, suet and raw beef pancreas. Glycosuria began in traces July 29, and by Aug. 3 had risen above 1%. Experiments with exercise were conducted at this time to show that the usual lowering of blood sugar occurs when there is no nerve supply to the pancreas remnant. The pancreatic graft meanwhile was plainly palpable as a soft mass emerging from under the muscle at the end

bearing the duct, and a wide area of skin was kept wet with the slightly turbid secretion from the duct, which was proved by tests to have a digestive action on starch and protein. The dog was killed Sept. 22, when barely able to stand, at a weight of 8.6 kilos.

The pancreas remnant was soft, lobulated and almost normal in appearance, and weighed 5.5 gm. It had no intraabdominal connections. The other viscera were negative to gross and microscopic examination, except for a moderately fatty liver and Armanni vacuolation in the kidneys. The pancreas remnant had evidently undergone atrophy only in small areas. Fifty slides, each bearing 3 or 4 sections, were examined in order to have all parts represented. In all but a few of these the parenchyma was beautifully normal, consisting of normal acini well filled with zymogen, with no signs of degeneration or fibrosis. Islands were abundant, but almost every cell was maximally vacuolated. The hydropic changes were so extreme and typical that they were used for one of the illustrations in paper I (Fig. 12.) There was also vacuolation in the small ducts and cell cords. The entrance of vessels and nerves from the surrounding tissue into the pancreas remnant could be demonstrated even with the naked eye. The microscope showed numerous normal intra-pancreatic ganglia.

Diabetes occurred here with an unusually large pancreas remnant, but as it began before the full isolation of the graft it can scarcely be attributed to this cause. It may rather be ascribed to inflammation or impaired nutrition of the graft shortly after operation. This experiment agrees with the preceding one, in that section of the nerves did not precipitate glycosuria even in an animal which was already mildly diabetic. It proves also that typical hydropic changes may occur in the islands when the pancreas remnant is isolated from all of its original extrinsic nerve supply and when the acinar tissue is normal.

Dog C3-88. — Male; mongrel; brown; age 4 years; medium nutrition; weight 10 kilos. May 3, 1916, removal of pancreatic tissue weighing 15 gm., leaving the uncinate process, estimated as about 1/3 of the gland, communicating with the main duct, also a separate remnant estimated at 1.25 gm. communicating with a lesser duct.

The dog thrived at an even weight, and operation on June 10 showed both pancreas remnants in excellent condition. A button of duodenum bearing the papilla of the pancreatic duct was excised, the duodenum repaired, the excised portion sutured into an opening in the skin, and the uncinate process transplanted under the skin, keeping its pedicle of inferior pancreaticoduodenal vessels and accompanying nerves.

The dog continued to thrive, as the small pancreas remnant secreting into the duodenum maintained digestion. July 11, the pedicle of the subcutaneous remnant was cut, and tissue weighing 3.9 gm. was removed from the end where the pedicle had formerly entered. This

tissue was microscopically normal in acini, islands and freedom from fibrosis.

The dog thrived and held weight as before. The pancreatic graft was palpable as a soft mass under the skin, apparently retaining its original size, and its secretion kept the entire abdominal skin wet. This large area remained hairless. The natural color of the skin was white, but along with thickening of the epidermis the irritation led to a remarkable blackish pigmentation. Microscopically there was great hyperplasia of epithelium and hypertrophy of the villi, by no means cancerous but yet suggesting some resemblance to cancer according to colleagues in the cancer service. The outer layers of the thickened epiderm peeled off rather easily in places, but there was no ulceration.

Aug. 3, 2.55 gm. of tissue was removed from the end of the graft to which the pedicle had formerly been attached, thus making an additional gap between it and any possible intra-abdominal connections. Blood vessels of surprising size, passing from the capsule of thickened subcutaneous tissue into the graft, bled freely when divided in this operation. The tissue removed was free from degeneration or fibrosis as before, and acini, islands and nerve ganglia were normal. This subcutaneous operation was of trivial character, and did not alter the animal's spirits or the taking of the regular diet. The entire graft, however, became swollen and hard by the next day, and on Aug. 5 a marked glycosuria appeared. This diminished to a faint reaction on Aug. 6 and then ceased. The observation seemed to afford an example of a transitory diabetes or lowering of tolerance due to pancreatitis, and also indicated that the prevention of diabetes depended more upon the large subcutaneous graft than upon the small remnant left beside the duodenum.

The graft quickly regained its soft consistency and continued to secrete juice freely upon the skin. Aug. 31, 0.15 gm. of tissue was removed from the small intra-abdominal remnant and 0.7 gm. from the graft. Both were microscopically normal, but islands were much more abundant in the graft than in the duodenal remnant.

No glycosuria ensued on lung and suet diet, which was adopted as a precaution during the period following operation, but a return to the former bread diet caused immediate heavy glycosuria. The dog was thus definitely diabetic. On the carbohydrate-free diet glycosuria remained absent but the nutrition was not as well maintained. By Sept. 15 the weight had fallen to 8.1 kilos and the dog was weak. The question presented itself whether the cachexia could be due to the prolonged loss of alkali in the pancreatic juice. The CO_2 capacity of the blood plasma by Van Slyke's method remained fully normal, and the giving of 5 gm. sodium bicarbonate daily brought no improvement. Any need of mineral salts was in fact probably well supplied by the bone-meal which the dog received liberally with the diet from the beginning.

Sept. 15, 0.3 gm. of tissue was removed from the duodenal pancreas remnant, and 1.4 gm. from the subcutaneous graft. Both remnants ap-

peared grossly in good condition. Microscopically the specimen from the duodenal remnant was normal as before, though containing only scarce and small islands. The graft specimen was taken from marginal tissue which was tightly adherent to the connective tissue capsule. Blood vessels, nerves and connective tissue from the capsule could be seen penetrating between the pancreatic lobules. The lobules were thus separated and enveloped by fibrous tissue, but this did not invade the lobules themselves and the parenchyma remained strictly normal. Islands were abundant and normal as before. In particular, hydropic changes were absent in both pancreas remnants.

After further loss of strength and refusal of food, the dog died in prolonged feeble convulsions on Sept. 19. The cause of death was undetermined, whether due to something connected with the experiment or possibly to rabies.

The duodenal pancreas remnant was normal in appearance and consistency, and weighed 1.5 gm. Microscopic search of the slides from different portions of it showed the same conditions as before. The scarcity and smallness of islands was characteristic of the entire remnant, but may be observed frequently in this part of the pancreas and therefore is not necessarily abnormal.

The subcutaneous graft appeared normal in most parts, but some areas were atrophic and the region of the recent operation was slightly inflamed. The weight was 4.25 gm. The blood supply from the surrounding capsule was easy to demonstrate, in the form not of mere capillaries but vessels of appreciable size. Microscopically, an abundance of fibrous tissue accompanied the ingrowth of vessels and nerves and was proliferating between the lobules. The lobules were not invaded, but in the atrophic areas they seemed to be strangulated and were undergoing degeneration. In most of the peripheral zone the parenchyma even when surrounded by fibrous tissue seemed to be normal, while the interior was free from fibrosis and normal in all respects. Islands were large and numerous and ganglia normal as before. Hydropic changes were also absent.

The experiment proved that when diabetic symptoms are prevented by diet, the islands remain free from vacuolation as usual both in a remnant retaining its normal connections and in another completely isolated from them.

Dog D4-12.—Male; mongrel; black and white; age 2 years; medium nutrition; weight 8.8 kilos. July 11, 1918, removal of pancreatic tissue weighing 13.7 gm. A remnant estimated at 2.1 gm. was left surrounding the small duct, and the uncinate process and part of the body, estimated at 11.5 gm., were left communicating with the main duct.

Aug. 15, the small remnant was found atrophic in appearance. The large remnant with the portion of duodenum bearing the opening of the pancreatic duct was used for a subcutaneous graft with the usual vascular pedicle.

By Aug. 29, the weight had fallen to 5.6 kilos through indigestion.

Operation on that day showed the duodenal remnant reduced to a sclerotic nodule, without duct communication. As sometimes happens, the tissue neighboring to the small duct and supposed to drain into it did not actually do so, and the cause of the emaciation was thus explained. This sclerotic remnant was removed. The subcutaneous graft appeared normal. Its pedicle was cut between ligatures, and 1.2 gm. of tissue was removed from the end where the pedicle had entered. Microscopically, the duodenal remnant consisted chiefly of fibrous tissue and remains of ducts, but a few small islands free from vacuolation were recognizable in the better preserved areas of parenchyma. The tissue from the graft was normal and free from fibrosis, with acini well filled with zymogen and islands abundant and normal.

Traces of glycosuria followed this operation on a diet of meat and raw beef pancreas, and increased when milk was added Sept. 1. Occasional traces returned as the diet was changed in various ways in the attempt to maintain nutrition, but for the most part glycosuria and hyperglycemia were suppressed by cachexia and were absent entirely after Sept. 23. Death occurred from weakness on Sept. 30, at a weight of 4.3 kilos.

The pancreatic graft was soft and normal in gross appearance, but weighed only 4.9 gm. Part of this loss of weight may have been associated with the general atrophy of organs from inanition, but part also had evidently been lost by necrosis due to inadequate blood supply of the end farthest from the duct. Microscopically the graft was almost free from fibrosis or degeneration. The acini were healthy in appearance and well filled with zymogen. Islands were large, numerous and free from vacuolation.

This experiment proved that the endocrine function of the pancreas could be at least partially performed by an isolated graft in the absence of any other pancreatic tissue, and that in the absence of any marked glycosuria the islands remained free from vacuolation as usual.

Dog E5-81. — Female; white bull terrier; age 8 to 10 years; medium nutrition; weight 15.25 kilos. May 8, 1917, removal of pancreatic tissue weighing 16.1 gm. A remnant estimated at 4.1 gm. was left about the smaller duct, and the uncinate process (size not estimated) was left communicating with the main duct.

June 1, the duct-bearing area of the duodenum was excised and a subcutaneous graft made of the uncinate process as usual.

The dog digested satisfactorily, but had poor spirits and appetite and accordingly lost weight. The transplanted button of duodenum had sloughed immediately after the last operation; the graft gradually stopped discharging secretion, and could be felt as a shrunken indurated mass under the skin. Intoxication from the pancreatic graft and its retained secretion was the probable cause of the ill health.

July 3, when the weight was 12.8 kilos, the duodenal pancreas remnant, which was slightly hardened, was removed with the exception of a

small piece estimated at 0.2 gm., which was left draining into the small duct in the hope that it might be of some small aid to digestion, while being almost negligible from the standpoint of diabetes. The subcutaneous graft was found in better condition than expected, its tissue being soft but tightly compressed by a firm connective tissue capsule. The greater portion of the graft, weighing 8 gm., was also removed, leaving the middle portion isolated from all intra-abdominal connections. Microscopically, the duodenal pancreas remnant was normal except for slight diffuse fibrosis. Its islands were scarce and small but otherwise normal. The subcutaneous graft was fibrous in its periphery but normal in the interior. The acini were well filled with zymogen. The islands, though not numerous or large, were more abundant than in the duodenal remnant, and were free from vacuolation.

Heavy glycosuria ensued on mixed diet. July 12 the weight was 11.5 kilos, and 0.45 gm. of tissue was removed from the subcutaneous graft. This was taken from the periphery and was found to consist chiefly of scar tissue. The parenchyma was in various stages of degeneration, but in the better preserved portions a few small islands could be recognized, which showed doubtful vacuolation of a minority of cells.

July 24 the weight was still 11.5 kilos, the glycosuria 5.1%, the plasma sugar 0.425%, and the dog was chloroformed on account of extreme weakness. The duodenal pancreas remnant weighed 0.2 gm., and the subcutaneous graft 0.9 gm. The former was slightly and the latter extensively fibrosed. Areas of well preserved parenchyma were found in both, containing not only normal appearing acini but also a fair number of small islands, with moderate vacuolation in a majority of their cells.

This experiment illustrated parallel progress of hydropic changes in two pancreas remnants, one left *in situ* and one isolated from all its old connections.

Dog E5-36.—Male; mongrel; yellow and white; age 5 years; excellent nutrition; weight 18 kilos. May 14, 1917, removal of splenic process and most of body of pancreas, weighing 25.1 gm. A remnant estimated at 3.6 gm. was left about the small duct, and the uncinate process (weight not estimated) was left communicating with the main duct.

June 1, a button of duodenum bearing the pancreatic duct was excised and a subcutaneous graft made of the uncinate process in the usual manner.

The dog retained liveliness but lost weight. Pigmentation began early in the abdominal skin irritated by the profuse discharge of pancreatic juice. July 3, when the weight was 14 kilos, the pedicle of the pancreatic graft was cut between ligatures, and tissue weighing 1 gm. was removed from this end of the graft. The cut surface of the graft bled freely on removal of this tissue, indicating a good circula-

tion from its new environment. The tissue removed was normal grossly and microscopically. Its islands were numerous but small, and their cells were pale but free from any true hydropic changes.

A trace of glycosuria was present in the hours following this operation, but could not be maintained by the feeding of maximal quantities of bread and soup and 100 gm. glucose daily. July 12, at a weight of 13.5 kilos, tissue weighing 1.9 gm. was removed from the end of the graft where the pedicle had formerly entered. Most of this was serially sectioned and no ganglia were found. There was the usual fibrous tissue invasion about the periphery, but the interior was normal in respect to both acini and islands.

July 27, when the weight was 13 kilos, the abdomen was opened and the duodenal pancreas remnant found apparently normal except for unexpected smallness, its weight being apparently about 0.6 gm. Its connection with a small duct was demonstrable, but it seemed probable that the rest of the tissue originally left had not drained into this duct and had disappeared accordingly. About $\frac{1}{3}$ of this remnant, 0.2 gm. by weight, was removed. After closure of the abdomen one end of the subcutaneous graft, weighing 9.8 gm., was removed, leaving the other end in communication with the duct. The skin and subcutaneous tissue about the graft were surprisingly vascular, and numerous little arteries spurted vigorously where normally none would have been encountered. Microscopically, the duodenal remnant showed only trivial fibrosis; the acini were normal, and the islands few but normal. No ganglia were encountered. The subcutaneous graft showed the usual entry of vessels and fibrous tissue about the periphery. Nerves were seen, presumably derived from the surroundings, though their course was not traced. Search of 45 slides revealed numerous ganglia, entirely normal in appearance. The interior portions of the parenchyma were strictly normal. Islands were rather scarce but normal and free from vacuolation.

The dog remained free from glycosuria and hyperglycemia on a diet of bread, milk and bone-meal. The duodenal mucosa surrounding the transplanted pancreatic duct remained red and healthy, and the duct continued to discharge juice freely. The thickening and pigmentation of the irritated abdominal skin became very marked, and microscopically the epithelial hyperplasia surpassed that of dog No. C3-88. A slow loss of weight and strength continued.

Aug. 21 the weight was 12.3 kilos, the plasma sugar 0.089%, and the CO₂ capacity of the plasma 66.4 vol. %. Most of the remaining pancreas graft was removed, leaving a small remnant at the end communicating with the duct. The tissue removed weighed 7.8 gm., and was normal both grossly and microscopically except for a narrow marginal zone. Islands were present in fair abundance and free from any suspicion of vacuolation.

Glycosuria was absent on a diet of 200 gm. beef lung, 100 gm. raw beef pancreas, bone-meal, bread and milk ad libitum, until the addition of 100 gm. glucose on Aug. 23. It then became heavy and remained so after withdrawal of the glucose on Aug. 25. Sept. 7 the

dog was still in excellent spirits but weighed only 10.2 kilos. On that date 0.2 gm. of tissue was removed from the duodenal pancreas remnant, which appeared normal. Also 1.9 gm. of normal appearing tissue was removed from the subcutaneous graft, still leaving the end in communication with the duct. Microscopically, the graft tissue was still normal in general architecture except for marginal fibrosis. The acini in some areas were moderately well filled but were nearly empty in others, as is often the case in cachexia. Numerous normal ganglia were present. Islands were fairly abundant, but a majority of their cells were markedly vacuolated. The tissue of the duodenal remnant showed only trivial fibrosis. The acini were normal, but on the whole contained less zymogen than those of the graft. No ganglia were found. Islands were extremely scarce; a few small remains were found in the last stages of hydropic degeneration, also a few tiny groups of apparently normal (presumably alpha) cells. The appearance was as though hydropic degeneration had progressed further than in the graft, but yet vacuolation of ducts was absent here as also in the graft.

The dog, too weak to survive the operation, ate 100 gm. of raw pancreas on Sept. 8 and was found dead on Sept. 9. The duodenal pancreas remnant weighed 0.35 gm., and the subcutaneous graft 2 gm. They were still normal in gross appearance, with scarcely any visible inflammation from the recent operation. Microscopically there was no important difference from the findings of Sept. 7.

The experiment corroborates the preceding observations of absence of hydropic degeneration with absence of diabetes and occurrence of hydropic degeneration with diabetes present, in both the remnant left *in situ* and the one isolated from all its former connections. The apparently different rate of progress of the hydropic change in the two remnants raises the question whether this difference may have been due to nervous influence. As the islands in the first place were fewer and smaller in the duodenal remnant than in the graft, and as a small remnant is exposed in greater degree than a large remnant to operative trauma which sensitizes to the hydropic change, it is difficult to assert that the different findings in these two remnants are attributable to a nervous factor. A better comparison is afforded by the larger experience in paper 1 of this series, which shows that the rate of hydropic change differs slightly between different remnants left *in situ* from causes not precisely controllable, and that the average rate of change in such remnants is about the same as in the isolated remnant in this case. It must therefore be concluded that the rate of hydropic change in this isolated remnant was not appreciably slowed by lack of a special nervous influence.

The rule in the graft experiments preceding the present one was that diabetes occurred with noticeably larger pancreas remnants than was customary after the usual form of operation which leaves the remnant *in situ*. Due regard was necessary for the fact that the transplanted remnants were specially subject to the disturbances of inflammation and of impaired circulation, and for the further fact that diabetes was occasionally found to result from similar disturbances when similarly large remnants were left *in situ*, as described in paper 6 of this series. Nevertheless the possibility remained open that the isolated remnants possessed a diminished anti-diabetogenic potency because of the lack of a special nervous control, and this doubt could be settled only by an example of normal internal secretory capacity in such an isolated graft. The present experiment is important as furnishing a fairly good example of this kind, probably on account of the rich blood supply to the graft. After the operation of Aug. 21 the total amount of pancreatic tissue represented in the two remnants combined was small enough that diabetes might have been expected under any conditions, and its slow and mild onset furnished evidence that the graft was opposing it as strongly as could be expected from any equal mass of pancreatic tissue. Altogether, therefore, the graft experiments afford interesting illustrations of the subnormal endocrine capacity of pancreatic tissue under unfavorable conditions even when it is normal in appearance and rich in islands, but they do not indicate the existence of any such endocrine deficiency in consequence of the lack of any specific nervous regulation.

Certain technical points may also be noticed in this experience. Maintenance of normal pancreatic structure over long periods is possible only with free drainage of the pancreatic juice, and the necessary patency of the duct can be maintained only if the expedient (long familiar to physiologists) of transplanting its duodenal orifice be adapted to this purpose. The health of the dog is best preserved if at the same time a small pancreas remnant is left secreting through the lesser duct to supply the needs of digestion.

The writer has tried devices such as imbedding the pancreas remnant in the mammary tissue of a female dog and anastomosing the duct with the orifice of a large teat, but only failure re-

sulted. The site of implantation, whether in the spleen or in any of the layers of the abdominal wall, seems to be immaterial; also a graft in the comparatively bloodless subcutaneous tissue of a male dog succeeds as well as one placed among the abundant mammary vessels of a female dog. The surrounding tissue reacts with inflammation and the development of a rich vascular supply; a capsule surrounds the graft and sends vessels and (presumably vasomotor) nerves into it, but yet it can be readily stripped out at any time. Though it is surprising what large masses of normal appearing pancreatic tissue can survive for months in the abdominal wall in this parasitic manner, it is probable that the ultimate fate of any such isolated graft must be degeneration and absorption.

The idea expressed by some authors that dogs may obtain some digestive benefit by licking the juice from a subcutaneous graft is purely imaginary, for every dog seems quickly to acquire such a distaste for the secretion that he refrains entirely from licking it. The irritation of the skin by the juice was observed to give rise to pigmentation only in certain individual animals.

Every step in the graft experiments is easy, and the experiments are difficult as a whole only because of the months of time that may be wasted if any one step fails or if the dog meets death from distemper or any accident. For this reason the investigation is tedious, and decisive results are generally obtained only at the price of a larger number of failures.

CONCLUSIONS

1. No influence of emotion upon the production of diabetes could be demonstrated in these experiments. In one instance a violent general traumatism seemed to activate a latent diabetes, but this effect was transitory.

2. The Claude Bernard piqure of the medulla, selected as the type of an irritative nervous lesion, seemed to be a genuine factor in producing diabetes in one predisposed dog, thus tending to confirm a previous single result of the same kind; but this question must be left open till some more effective means of stimulation can be employed, and the newer knowledge of diabetes necessitates very strict proof before the

existence of an irritative nervous factor in the etiology can be accepted.

3. Complete separation of a pancreas remnant from its original nerve supply fails to give rise to diabetes or any demonstrable lowering of assimilation. The full endocrine potency may apparently be maintained without stimulation or regulation from any special nervous centers.

4. Such isolation of the pancreas remnant also fails to affect either the occurrence or the rate of hydropic degeneration in the islands, which runs parallel with the course of the diabetes the same as when the nerve supply is left undisturbed.

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EXPERIMENTAL STUDIES IN DIABETES

SERIES III. THE PATHOLOGY OF DIABETES

4. THE ROLE OF HYPERGLYCEMIA IN THE PRODUCTION OF HYDROPIIC DEGENERATION OF ISLANDS.

BY FREDERICK M. ALLEN.

*From the Hospital of the Rockefeller Institute for Medical Research,
New York.*

As it is evident from the preceding paper that humoral agencies must be able to produce the hydropic changes in the pancreatic islands, the first possibility which naturally suggests itself is that these changes may be due to direct stimulation by the excess of circulating food substances. Numerous observations (some of which are summarized in the tables in paper 1 of this series) have shown no difference in the island changes with presence or absence of acidosis or lipemia, and there is no evidence for connecting these changes directly with fat metabolism. As mentioned in paper 1, these hydropic changes may occur with prolonged hyperglycemia even without glycosuria. It may appear a plausible hypothesis that the circulating glucose itself is the stimulus which drives the island cells to over-function. A series of experiments were therefore conducted to test this hypothesis.

I. INFLUENCE OF BRIEF HYPERGLYCEMIA

Previous experience¹ had shown that glucose doses given to normal animals before partial pancreatectomy failed to produce visible changes in the pancreas or increase the tendency to diabetes. Similar experiments were therefore performed in animals which had already been depancreatized nearly or quite to the point of diabetes, with the idea that they might be more readily subject to such changes.

Dog B2-71, a female yellow mongrel weighing 14 kilos, became dia-

betic after removal of 9/10 of the pancreas on June 3, 1914. The diabetes was kept mostly under dietary control while the dog was used for various experiments, but the general progress was slowly downward, so that by Nov. 1915 traces of glycosuria were frequent on a low protein-fat diet in an emaciated condition at a weight of 7 kilos. On the afternoon of Nov. 24, 0.4 gm. of pancreatic tissue was removed and both jugular veins exposed in a brief operation under ether. Beginning at 4 P.M., when the animal's behavior was again normal, intermittent injections were given amounting to a total of 100 gm. glucose in 10% solution, half subcutaneously and half intravenously. Blood samples taken at hourly intervals proved that the plasma sugar was kept between 0.4 and 0.7 per cent. The animal was killed for autopsy at 1 A.M. Moderate vacuolation was present in the island cells, but there was no perceptible difference in its degree in the tissue removed at operation and in that at autopsy.

Dog B2-87, a male Dalmatian, aged 2 years and weighing 19 kilos, after removal of 4/5 of the pancreas on April 9, 1915 could not be made diabetic by the heaviest glucose feeding (up to 400 gm. daily) prolonged to June 7. The diet for the next month was plain bread and soup. July 8, 200 gm. glucose in 50 per cent solution was injected subcutaneously at 2 P.M. The subsequent tests showed not only the usual marked hyperglycemia but also concentration of the blood as indicated by hemoglobin and corpuscle volume estimations. The experiment was planned to produce severe osmotic disturbance, and death occurred presumably from this cause at 7 P.M. The pancreas remnant and its islands were normal not only in routine stains but also in a series of 24 slides prepared with the special granule stains. Here neither the physiological nor the osmotic influence of the excess of sugar sufficed to produce vacuolation of the islands.

Dog C3-77, a female brown and white mongrel, aged 1 year and weighing 10.5 kilos, underwent partial pancreatectomy on April 13, 1916. The tissue removed weighed 21.8 gm. The remnant was estimated at 1.1 gm. (1/21). The glycosuria was stopped by fasting to April 23. It was kept absent thereafter on very low protein diets, but distemper developed. May 7, 0.25 gm. of pancreas tissue was removed at 2 P.M., and continuous intravenous infusion of 10 per cent glucose solution was begun at 2:30. In addition, 500 cc. was given subcutaneously. No blood analyses were made, but there was continuous glycosuria, the total urine volume being 680 cc., containing 36.4 gm. sugar. In addition, liquid feces were passed abundantly, which gave qualitative sugar tests, and a specimen cleared with colloidal iron and titrated with Benedict's copper solution showed a sugar content of 0.485 per cent. The general condition of the animal or the existence of diarrhea due to distemper may have occasioned this unusual intestinal excretion. By 9:30 P.M. 2 liters of 10 per cent glucose solution had been injected intravenously, and the animal was killed for autopsy. Slight vacuolation was present in a minority of island cells, but apparently more in the tissue taken at operation than in that at autopsy.

Dog C3-78, a brown and white female mongrel, aged 4 or 5 years and weighing 17 kilos, was subjected to removal of 5/6 of the pancreas on April 13, 1916. Glycosuria was absent on bread diet, but was present with addition of 100 gm. glucose on April 25. April 26, 100 gm. glucose in 500 cc. solution was given by stomach tube at 10 A.M., with resultant glycosuria, and at 2 P.M. 0.6 gm. of pancreas tissue was removed, producing mild diabetes. No hydropic changes were demonstrable in the tissue removed, in consequence of 2 days of sugar feeding in an animal so close to diabetes.

Dog G7-08 was a brindle male bull terrier aged 3 or 4 years, weighing 12.5 kilos. June 21, 1918, pancreatic tissue weighing 31.7 gm. was removed, leaving a remnant about main duct estimated at 2 gm. (1/17). On fasting thereafter glycosuria remained absent. June 25, 0.1 gm. additional tissue was removed. Glycosuria was found immediately after this operation, and the plasma sugar the next morning was 0.228 per cent. The hyperglycemia was increased by the intravenous injection of 40 gm. of glucose during the day, and reached a maximum of 0.65 per cent. On June 27, without further injections, the blood sugar gradually fell from 0.164 per cent at 8 A.M. to 0.149 per cent at 3 P.M. The dog was then killed and autopsied. There were no definite hydropic changes in the pancreas. In the small wedge of tissue removed at operation, the superficial portion showed recent inflammation and corresponding pallor of both acini and islands, but the deeper portions were strictly normal. The findings in the tissue at autopsy were the same.

Dog F6-41, a black and white male mongrel aged 3 years and weighing 9.7 kilos, was subjected to the removal of 14/15 of the pancreas on March 20, 1918, leaving a remnant estimated at 1.8 gm. Glycosuria remained absent on continuous fasting. March 27, 0.15 gm. additional pancreatic tissue was removed for examination. March 30, after continued absence of glycosuria on fasting, intravenous injections were begun as follows:

10:30 A.M., plasma sugar 0.143%. Injection of 50 gm. glucose in 30% solution into jugular. Plasma sugar 5 minutes after 1.11%.

3 P.M. Injected 100 cc. of 30% glucose solution into jugular.
Rectal temperature 38.6° C.

8 P.M. Plasma sugar 0.164%. Injected 250 cc. 30% glucose solution into jugular. No symptoms except thirst. Total glucose excretion up to this time 24 gm.

March 31, 9:30 A.M. Plasma sugar 0.152%. Total glucose excretion since 8 P.M. 66.5 gm. Injected 150 cc. of 30% glucose solution into jugular.

12 Noon, Injected 150 cc. 30% solution.

5 P.M. " 150 " 40% "

10 P.M. " 100 " 40% "

Great polyuria and glycosuria; urine partly lost.
Rectal temp. 40° C. Vomiting of greenish mucous liquid which reduces copper rather strongly.
Plasma sugar immediately after last injection 2.22%.

The dog was killed at 1 A.M. (April 1) when very weak, though still conscious and able to stand. The gross autopsy was negative. The pancreas remnant weighed 2.3 gm. Microscopically in routine stains the liver appeared extremely fatty, as judged by the marked vacuolation. The kidneys were normal, without Armanni changes. The other organs were negative. The pancreas specimens both from March 27 and from the autopsy were normal except for slight pallor in many island cells, which was no greater at autopsy than at operation. In stains for glycogen by Best's carmine, the liver and heart muscle were crowded with red granules, the pancreas and skeletal muscle contained none, and the kidney showed the barest traces in Henle's tubules.

In this animal a week of diabetes without glycosuria produced probable slight hydropic changes, which were not altered by 38 hours of intense hyperglycemia and glycosuria. The fattiness of the liver is not unusual in such a case, but the readiness with which it appeared to form glycogen is remarkable. It is well known that in diabetes the heart muscle may be rich in glycogen when the skeletal muscle contains none. It might be interesting to know the time limits of the Armanni change in the kidney. The present observation may perhaps indicate that several days of hyperglycemia or glycosuria may be required for its occurrence.

Dog G7-35, a male spaniel mongrel, weighing 12.6 kilos, on June 21, 1918 underwent removal of 12/13 of the pancreas, leaving a remnant estimated at 2.4 gm. Glycosuria remained absent on fasting. June 25, 0.1 gm. additional tissue was removed. Beginning June 26, when the plasma sugar was 0.131%, occasional intravenous injections of 20% glucose solution were kept up both day and night till 1 A.M., June 29, when the dog died. The general procedure and results were similar to those in dog F6-41. The highest plasma sugar obtained immediately after an injection was 2.63%, and the lowest level to which it was permitted to fall was 0.244%. The autopsy was negative except for some congestion of the brain and meninges.

The pancreas was normal at both operation and autopsy, without signs of hydropic change. This slight difference from the preceding animal may be explainable by the slightly larger size of the remnant. The kidneys showed congestion and small interstitial hemorrhages, and very slight Armanni changes. The liver appeared congested and moderately fatty. The adrenals took a pale stain, the cells appeared small and shrunken, and there was less than the usual lipoid vacuolation of the cells in the cortex. No glycogen stains were made.

These experiments confirm the observations in paper 1 of this series that several days, generally 4 at least, are necessary

for the beginning of hydropic changes or a distinct progress of existing changes, even when the diabetes is severe enough to insure maximal rapidity of the alterations. The experiments exclude a supposition that any such changes might be produced within a few hours by sufficiently intense hyperglycemia resulting from glucose feedings or injections, even if the animals are already diabetic and some degree of vacuolation is already present in the islands.

II. INFLUENCE OF LONGER HYPERGLYCEMIA

Dog B2-05, a white female mongrel aged 9 months and weighing 6.5 kilos, on Nov. 6, 1913 underwent removal of 10.3 gm. of pancreatic tissue, leaving a remnant estimated at 1.2 gm. (about 1/10). Glycosuria was absent on meat diet, but with a change to bread and milk on Nov. 14 there was 7 per cent of sugar in 300 cc. of urine. This glycosuria steadily diminished to 0.9 per cent on Nov. 18 and was evidently on the point of disappearing. After removal of 0.5 gm. pancreas tissue on Nov. 18, glycosuria was present on meat diet, but distemper and loss of appetite stopped the diabetes. There was sugar freedom and gradual emaciation from Nov. 22 to death on Dec. 11. The pancreas remnant at autopsy, normal in appearance, weighed 1.25 gm.

The tissue removed Nov. 18 was normal except for marked swelling and vacuolation of a few cells in the majority of islands. Recovery from the diabetes, of which the disappearing glycosuria was a sure indication, was evidently in progress even in the presence of this vacuolation. The latter also was presumably receding rather than advancing, even with hyperglycemia and glycosuria present. The subsequent clearing up of both diabetic symptoms and vacuolation is merely the usual result of undernutrition.

Dog C3-00, a white female mongrel aged 5 years and weighing 4.5 kilos, underwent removal of 9/10 of the pancreas on May 6, 1915. Glycosuria was kept mostly under control by restricted protein diet up to July 7, though there was probably hyperglycemia part of the time. July 8 to 11 there was heavy glycosuria on bread diet, and no glycosuria July 12 and 13 on meat diet. July 13, 0.15 gm. of pancreas tissue was removed as a specimen. Thereafter the animal was kept on low meat diet, so regulated that glycosuria was continuously absent but hyperglycemia continuously present. At least one plasma sugar analysis was performed daily. There was evidently downward progress, for on the identical diet the plasma sugar before feeding was 0.135 per cent on Aug. 10, 0.182% on Aug. 15, and 0.232% on Aug. 21. The dog was killed for autopsy Aug. 21.

The pancreas specimens furnished some of the examples of hydropic change shown in paper 2 of this series. The renal impermeability which prevents glycosuria evidently does not prevent island degeneration or the attendant loss of tolerance, and this observation has

a direct application to clinical treatment. The vacuolation found on July 13 was also evidently due in part to the state of simple hyperglycemia, for experiences previously mentioned indicate that the 3 days of glycosuria could not alone have sufficed to produce it.

Dog C3-20, a brown male mongrel aged 8 years, weighing 24 kilos, was subjected to removal of 4/5 of the pancreas on June 24, 1915, leaving a remnant estimated at 11.5 gm. Glycosuria was then absent on a diet of bread and soup with 300 gm. glucose daily. July 16, 2.2 gm. additional pancreatic tissue was removed. Thereafter the same diet kept up glycosuria of less than 1% daily. A probable continuity of hyperglycemia was indicated by a single plasma sugar analysis of 0.167% before feeding on July 21. July 30, 1.1 gm. additional pancreatic tissue was removed. Afterward a similar slight glycosuria could be maintained with smaller quantities of glucose. It continued also when glucose was stopped on Aug. 6, but diminished and ceased on Aug. 14. Aug. 15, the plasma sugar was 0.143% before feeding. On the morning of Aug. 16 it was only 0.088%. The diabetes therefore was evidently tending to clear up. Aug. 16, 0.6 gm. pancreatic tissue was removed. The weight, which by this time had fallen to 21.3 kilos, was then built up by a carbohydrate-free diet of beef lung and suet. Sept. 29, at a body weight of 24.9 kilos, the plasma sugar was 0.122% before feeding, but there was a hyperglycemic curve during digestion, the highest point being 0.161%. Oct. 23, when the weight had reached 25.8 kilos, glycosuria of 1.1% in 620 cc. of urine appeared, and was checked by 2 days of fasting. On the same diet it returned Nov. 1. On that date 1.4 gm. of pancreatic tissue was removed. Heavy glycosuria, up to 5%, followed. The dog was killed Nov. 3 on account of hernia of the wound. The pancreas remnant, normal in appearance and consistency, weighed 14.2 gm. The urine in the bladder contained 5.9% glucose.

The tissue removed July 16 was normal. Glucose feeding for 3 weeks had therefore failed to produce hydropic changes, though there is no proof of any marked hyperglycemia.

The tissue removed July 30 was also normal by both routine and granule stains. Glycosuria and hyperglycemia for 2 weeks, in an animal which was proved by its high tolerance be non-diabetic, therefore had failed to produce vacuolation.

The tissue removed Aug. 16 showed distinct vacuolation. This was evidently produced by 2 weeks of hyperglycemia and glycosuria in an animal with very mild or transitory diabetes. A rise of tolerance was also indicated notwithstanding this vacuolation.

The tissue removed Nov. 1 was characterized by fewness and smallness of islands. These showed slight but distinct hydropic changes, evidently associated with the prolonged hyperglycemia without glycosuria. The slow degeneration of islands also explained the decline of tolerance, so that glycosuria finally occurred on protein-fat diet.

The tissue at autopsy was indistinguishable from that of Nov. 1, two days of intense diabetes being too brief for perceptible effect.

Dog C3-27, a female mongrel aged 4 years, weighing 16.25 kilos, underwent removal of 8/9 of the pancreas July 8, 1915. Mild diabetes resulted, but owing to dietary control true recovery had taken place by Feb. 1916, so that a gain of weight to 20 kilos and the heaviest bread and glucose feeding failed to produce more than slight transitory glycosuria. This carbohydrate program began Feb. 10. On Feb. 11 the glycosuria was 0.73% with plasma sugar 0.214%. Similar hyperglycemia and glycosuria were maintained by gradually increasing the glucose to 400 gm. daily till March 9, when the appetite failed. On that date the removal of 0.9 gm. of pancreas tissue brought on diabetes, and the dog was subsequently used for an acidosis experiment.

The tissue removed was normal, without vacuolation in the islands. Nearly a month of hyperglycemia and glycosuria had therefore failed to produce hydropic changes in a non-diabetic animal, even though diabetes had been present some months before and could be brought back by the removal of very little additional tissue.

Dog D4-29, a spotted mongrel aged 2 years and weighing 11.5 kilos, underwent removal of 7/8 of the pancreas on Sept. 28, 1916, leaving a remnant estimated at 3.8 gm. Feeding with bread and soup and 100 gm. glucose was begun the next day, so as to maintain heavy glycosuria (2 to 4%). By Oct. 3 it had become impossible to keep up the glycosuria throughout the 24 hours, notwithstanding the addition of meat and suet to the diet and increase of glucose to 150 gm., which was as much as the dog would take. Oct. 4, a plasma sugar curve was obtained. This started at 0.093% before feeding at 10:30 A.M., rose to 0.307% at 11:45 A.M. and to 0.322% at 2 P.M., then fell gradually to 0.12% at 9 P.M. Specimens of urine during this time contained 1.8 to 5.25% sugar, but there was no glycosuria during the night. Oct. 9, a higher curve was obtained, starting at 0.12%, rising in 1 hour to 0.357%, in 2 hours to 0.445%, and holding a high level in the later tests, so that by 5 P.M. it was still 0.322%. Curves obtained similarly by hourly or 2-hourly tests on Oct. 10 and 11 rose only to 0.278%, owing to failing digestion. Also the duration of hyperglycemia diminished; e.g., at 10:30 P.M. the plasma sugar on Oct. 10 was 0.20%, on Oct. 11, 0.138%, on Oct. 12, 0.09%. Oct. 14, the curve was still between 0.20 and 0.27% throughout the day, falling by 7 P.M. to 0.189%.

Oct. 16, 0.65 gm. of pancreatic tissue was removed, and the former diet resumed the next day. The previous history was repeated, namely high glycosuria and hyperglycemia at first, falling lower on the succeeding days, and not continuing throughout the 24 hours. In the last curve on Oct. 24, there was slight hyperglycemia of 0.143% before feeding, but the highest figure was 0.232% after feeding. The dog met death by accident on Oct. 28, when it seemed still uncertain whether the diabetes could be made permanent without another operation or not.

The pancreas remnant, appearing normal and free from fibrosis, weighed 4.6 gm. It contained an abundance of large islands, and the hypertrophy may have played a part in the resistance to diabetes.

Vacuolation was entirely absent in the tissue removed Oct. 16 and also in that at autopsy.

There had been here 1 month during which glycosuria and marked hyperglycemia had been present every day but had seldom continued through the night. The islands seemed able to carry this burden successfully and showed no signs of breaking under the strain.

Dog D4-52, a yellow and white female mongrel aged 3 years and weighing 12 kilos, was subjected to removal of 7/8 of the pancreas on June 27, 1917, leaving a remnant estimated at 3.4 gm. Glycosuria was heavy at first on bread diet, later with addition of glucose up to 200 gm. daily, but diminished and ceased July 11. July 12, 0.35 gm. of pancreatic tissue was removed, and the same diet then produced glycosuria on only 2 days. July 20, 0.2 gm. additional tissue was removed, and no glycosuria could yet be maintained. After removal of 0.3 gm. additional tissue on Aug. 3, bread diet caused no glycosuria, but with addition of 200 gm. of glucose on Aug. 8 heavy glycosuria began, but diminished and ceased Aug. 13. The further record has been given elsewhere². It showed that the hyperglycemia from the feeding of 300 gm. bread and 200 gm. glucose on Aug. 8 and 15 was brief, lasting less than 6-1/2 hours. Nevertheless, continuance of simple bread diet gradually broke down the tolerance so that glycosuria began Oct. 10 and protein-fat diets were necessary thereafter.

The tissue removed July 12 contained abundant large islands, with very slight hydropic changes in a few cells. These may be associated with the heavy glycosuria which at first followed the operation of June 27. As the diabetes tended to clear up, it is probable that these hydropic changes were receding.

The tissue removed July 20 was free from hydropic changes. The amount of tissue removed was not sufficient to overcome the tendency to recovery. Glycosuria became more difficult, and correspondingly the vacuolation in the islands cleared up.

The tissue removed Aug. 3 showed slightly greater vacuolation than on July 12. The diminishing glycosuria and hyperglycemia in the tests of Aug. 8 and 15 may be explained partly by indigestion and diarrhea, and partly by the temporary maintenance of function by the islands at the price of injurious overwork. Indigestion necessitated stopping the glucose, but the bread diet sufficed to continued the breakdown of the islands at a slower rate, so that frank diabetes resulted.

The record of *Dog D4-69* has been previously given³. The tissue from all the operations there mentioned showed suspicious pallor of some island cells, but it could not be decided whether this was an accidental appearance or a very slight thinning of cytoplasm corresponding to the heavily taxed carbohydrate assimilation. Hyperglycemia and more or less glycosuria continuing most of the time through 6 months failed at any rate to cause any marked vacuolation of islands, evidently because the dog was not diabetic and the strain imposed by the combination of strong digestion and weakened assimilation was not sufficient for any structural breakdown of the islands. The final operation brought on diabetes, but specimens were not obtained thereafter.

Several other examples of either presence or absence of hydropic changes with hyperglycemia and glycosuria on prolonged starch and sugar feeding are given in paper 2 of series 1.⁴

III. REDUCTION OF BLOOD SUGAR WITH PHLORIZIN

Dog E5-96.—Male, mongrel, yellow and white, age 5 years, good condition, weight 16.75 kilos. Sept. 7, 1917, removal of pancreatic tissue weighing 29.25 gm. Remnant about main duct estimated at 0.78 gm. (1/38-1/39). Three hours before operation, 0.2 gm. phlorizin in olive oil was injected subcutaneously. Immediately after operation the plasma sugar was 0.175%. The next morning it was 0.125%, and 0.2 gm. phlorizin was again injected. Heavy glycosuria and ketonuria were maintained continuously. Injections of 0.5 gm. phlorizin were given on Sept. 9 and 10. 100 gm. raw beef pancreas was fed Sept. 9; otherwise all food was refused. The plasma sugar record was as follows: Sept. 9, 0.08%; Sept. 10, 0.05%; Sept. 11, 0.068%; Sept. 12, 0.079%. The dog was chloroformed Sept. 13 when moribund. The plasma sugar of the autopsy blood was 0.20%. The pancreas remnant weighed 2.0 gm. The gross autopsy was otherwise negative. Microscopically, there were slight Armanni changes in the kidneys and incipient vacuolation in the pancreatic islands.

Dog E5-99.—Male bulldog, age 4 years, good condition, weight 16 kilos. Sept 28, 1917, removal of pancreatic tissue weighing 26.2 gm. Remnant about main duct estimated at 1.13 gm. (1/24). Half an hour before operation, 0.5 gm. phlorizin in oil suspension was injected subcutaneously. Immediately after operation the plasma sugar was 0.170%. At 9 A.M. Sept. 29 the plasma sugar was 0.075%, and the urinary sugar up to this time was 26.4 gm. The subsequent record is shown in Table I.

TABLE I.
*Dog E5-99.**

Date.	Weight Kgm.	Plasma sugar, %	Urine			Phlorizin sub.cut., gm	Diet.
			Sugar, gm.	Total N. gm.	D N Ratio		
1917							
Sep. 30	16.0	0.075	23.64	7.80	3.04	0.2	Fasting.
Oct. 1	17.82	4.68	3.81	200 gm. lung
" 2	0.076	44.80	14.52	3.08	400 gm. "
" 3	0.650	52.20	16.84	3.10	0.2	600 gm. "
" 4	60.70	17.68	3.44	800 gm. "
" 5	0.060	64.20	17.60	3.67	" "
" 6	37.00	12.08	3.07	" "
" 7	16.50	10.75	1.53	0.2	" "
" 8	86.60	24.60	3.52	" "
" 9	0.94	22.20	11.92	1.86	0.2	" "
" 10	13.3	59.80	18.04	3.23	" "
" 11	0.129	21.95	10.50	2.08	0.5	" "
" 12	47.70	21.60	2.21	" "
" 13	0.051	24.60	6.83	3.60	0.2	" "
" 14	43.30	24.72	1.75	" "
" 15	0.106	35.30	11.16	3.16	0.3	" "
" 16	22.40	10.85	2.07	" "
" 17	0.105	35.60	14.12	2.52	0.3	" "
" 18	48.80	15.96	3.06	" "
" 19	12.8	18.3	7.20	2.54	0.3	" "
" 20	16.7	" "
" 21	No Urine	" "
" 22	73.40	0.5	" "
" 23	52.80	" "
" 24	11.1	0.077	12.00	Fasting. Removal of 0.22gm. of additional pancreatic tissue
" 25	29.5	0.3	800 gm. lung
" 26	0.078	45.7	" "
" 27	16.00	7.90	2.02	" "
" 28	14.90	" "
" 29	0.143	10.50	0.5	" "
" 30	0.103	30.20	" "
" 31	0.112	25.40	0.5	" "
Nov. 1	9.0	24.70	" "
" 2	11.90	" "
" 3	18.10	" "
" 4	5.40	" "

* The dog was not catheterized. The deficit of urinary nitrogen as compared with the food was due to poor digestion.

The pancreatic tissue removed Oct. 23 contained only rare small

groups of normal appearing island cells, presumably surviving A cells. There were no islands in the ordinary sense, also no vacuolated island or duct cells.

The findings at autopsy were similar, except for widespread vacuolation of small ducts and cell-cords which seemed to be ramifying in unusual numbers throughout the tissue.

TABLE II.
*Dog F6-01.**

Date	Weight Kgms.	Plasma Sugar, %	Urinary Sugar gm.	Urinary Nitrogen gm.	D/N Ratio	Phlorizin Subcut., gm.	Remarks.
1917							
Nov. 15	19.75	17.44	5.28	3.30	0.5	Fed 800gm. lung and 50gm suet
" 16	31.20	13.13	2.48	" " " " "
" 17	18.59	0.5	" " " " "
" 18	21.85	25.08	0.87	" " " " "
" 19	19.50	15.60	1.25	" " " " "
" 20	3.80	8.20	0.46	" " " " "
" 21	19.00	0.155	23.76	0.5	Not fed. Removal of pancreatic tissue weighing 49.2gm. Remnant about main duct estimated at 3.7 gm. (1/14-1/15)
" 22	13.40	4.00	3.34	Not fed.
" 23	21.00	5.94	3.54	Fed 800gm. lung and 50gm suet
" 24	0.122	22.50	9.52	2.36	0.5	" " " " "
" 25	25.20	7.14	3.56	Refuses all food.
" 26	17.00	0.082	10.20	3.96	2.58	Not fed. Pancreas remnant found inflamed. 1 gm. of additional tissue removed.
" 27	5.60	2.40	2.33	0.5	Not fed.
" 28	40.30	9.18	4.39	Given 500cc. saline subcut.
" 29	0.052	15.28	6.08	2.51	" " " "
" 30	15.00	0.069	36.40	" " " "

* The dog was not catheterized. The low urinary nitrogens after Nov. 21 are probably due to indigestion and extreme cachexia; also in this condition more or less urine was absorbed by the animal's long hair, so that the record is given chiefly as affording some idea of the D:N ratios.

The tissue of dog F6-01 from the operation of Nov. 21 was normal, phlorizin and the glycosuria caused by it having as usual no effect upon the pancreas.

The tissue of Nov. 26 showed marginal inflammation, with no islands in the inflamed areas. The deeper portions were free from inflammation and contained normal acini and islands, without vacuolation.

The pancreas remnant at autopsy weighed 2.65 gm., after evacuation of a small abscess. There was inflammatory infiltration everywhere

among the acini, and no islands could be identified. Moderate Armanni changes were found in the kidneys with ordinary stains, but very little glycogen appeared in the vacuolated cells with carmine stains, and none in some of them. The vacuolation was therefore probably due chiefly to fat, though no fat stains were made.

The dog's diet up to Nov. 21 had been 800 gm. of beef lung daily, but after that all food was refused. In view of the size of the pancreas remnant, together with the fasting and cachexia, it is improbable that any active diabetes existed. At any rate, 12 days of phlorizin glycosuria and a 5 day period after partial pancreatectomy failed to produce hydropic changes in the tissue of Nov. 26.

TABLE III.
*Dog F6-02.**

Date	Weight <i>Kgm.</i>	Plasma Sugar, %	Urinary Sugar gm.	Urinary Nitrogen gm.	D:N Ratio	Phlorizin gm.	Remarks
<i>1917</i>							
Nov. 15	18.25	21.28	7.20	2.96	0.5	Fed 800gm. lung and 50gm suet
" 16	27.00	20.61	1.36	" " " " "
" 17	4.80	13.96	0.5	" " " " "
" 18	18.92	17.38	1.09	" " " " "
" 19	25.30	19.08	1.33	" " " " "
" 20	11.40	14.12	2.77	" " " " "
" 21	17.50	0.100	Faint	9.40	0.5	Not fed. Removal of 36.3 gm. of pancreatic tissue. Remnant about main duct estimated at 2.3 gm. (1/16-1/17.)
" 22	15.75	7.95	1.98	Not fed.
" 23	16.47	8.37	1.97	" "
" 24	0.090	26.16	15.12	1.73	0.5	" "
" 25	54.00	15.90	3.40	" "
" 26	0.118	60.48	18.84	3.22	" "
" 27	30.00	11.20	2.68	0.5	" "
" 28	40.00	8.80	4.55	Given 500cc. saline subcut.
" 29	15.84	5.10	3.11	Not fed.
" 30	0.164	33.00	7.92	4.17	0.5	" "
Dec. 1	21.00	7.00	3.00	Given 500cc. saline subcut.
" 2	8.61	2.31	3.73	Not fed.
" 3	13.15	0.037	36.00	10.92	3.29	Given 500cc. saline subcut.
" 4	25.20	7.56	3.33	Not fed.
" 5	12.50	0.132	mod.	5.80	0.5	Not fed. Removal of 0.5 gm. of additional pancreatic tissue.
" 6	14.70	1.35	10.90	Not fed.
" 7	34.38	10.08	3.41	" "
" 8	40.50	7.92	5.12	0.5	" "
" 9	0.112	12.80	4.96	2.58	" "
" 10	18.42	4.32	4.27	" "
" 11	10.20	0.227	Faint	Died 10:00 am.

* Dog not catheterized.

Dog F6-02 received a diet of 800 gm. beef lung and 50 gm. suet before operation, but refused or vomited almost everything thereafter.

The tissue removed Nov. 21 was normal in both acini and islands, the effect of phlorizin being negative as usual.

The tissue removed Dec. 5 showed no signs of inflammation. The acini were normal and about half full of zymogen. Islands were present in moderate number and size, and showed early vacuolation.

The pancreas remnant at autopsy weighed 1.8 gm. Part of it contained parenchyma with inflammatory infiltration and no discoverable islands. The greater portion was free from inflammation. The acini were nearly empty but otherwise normal. The hydropic change in the islands was somewhat more advanced, and they seemed diminished in size and number. There was also considerable vacuolation in small ducts and cell cords. Stains with Best's carmine showed the usual absence of glycogen in the pancreas. The liver cells were vacuolated, especially toward the center of the lobules, presumably with fat, but contained no visible glycogen. The leukocytes everywhere were also glycogen free, corresponding to the hypoglycemia. The Armanni change in the kidneys was very marked, but the glycogen granulation was located around rather than in the vacuoles of the Henle tube cells.

SUMMARY AND CONCLUSIONS

1. Intense hyperglycemia (about 2 per cent. maximum) maintained during brief periods (3 to 38 hours) by administration of glucose intravenously and otherwise does not produce vacuolation in the pancreatic islands of non-diabetic animals or perceptible increase of an existing vacuolation in the islands of diabetic animals. Apparently the time limit of 4 days or more, observed in paper 1 as necessary for the beginning of any decided hydropic changes, cannot be greatly shortened by such an artificial elevation of hyperglycemia or glycosuria.

2. When animals have been brought close to diabetes by partial pancreatectomy, so that removal of perhaps a fraction of a gram of additional pancreatic tissue will suffice to make them diabetic, more or less continuous hyperglycemia and glycosuria can sometimes be maintained through several weeks or months by the highest possible diets of bread and glucose, but no vacuolation of islands results.

3. Occasional animals develop transitory diabetes after operation, as judged by the ease with which hyperglycemia and glycosuria are produced by bread diets with or without glucose, but later tend to recover, presumably through ana-

tomic or functional repair or hyperplasia in the pancreas remnant. Slight vacuolation of islands may be found in this early stage, but this clears up even though the hyperglycemia and glycosuria be prolonged further by massive doses of glucose.

4. Vacuolation of islands occurs in some diabetic animals with prolonged hyperglycemia without glycosuria.

5. Phlorizin dosage does not produce hydropic degeneration of the islands of non-diabetic animals, and does not prevent such degeneration in the islands of diabetic animals even though the blood sugar be kept continuously at or below a normal level.

6. The humoral stimulus to hydropic degeneration, indicated by the results of the preceding paper, therefore cannot be the excess of blood sugar, but must be something deeper or more specific in connection with the diabetes. Though only traces of their internal secretion can be supposed to exist in the blood, it is conceivable that the islands may be sensitive to a deficiency of the circulating hormone itself. This question, which suggests a secretory regulation on a principle resembling mass action, as also the possible nervous control by the intrapancreatic ganglia, are matters of pure speculation at present.

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EXPERIMENTAL STUDIES IN DIABETES.

SERIES III. THE PATHOLOGY OF DIABETES

5. THE INFLUENCE OF CIRCULATORY ALTERATIONS UPON EXPERIMENTAL DIABETES

BY FREDERICK M. ALLEN M.D.

*From the Hospital of the Rockefeller Institute for Medical Research,
New York.*

The possibility has occasionally been suggested in clinical literature that certain cases of diabetes may be due to arteriosclerosis involving the pancreatic circulation. Also, one plausible reason for the subnormal endocrine function of many pancreatic grafts observed in paper No. 3, manifested by the occurrence of diabetes with unusually large pancreas remnants, may be found in the abnormal character of the blood supply of such isolated grafts. From a broad standpoint, it may be readily recognized that the islands of Langerhans are provided anatomically with a liberal vascular supply, as though they might require a rather abundant flow of blood, but nothing at all is known of the circulatory conditions that may favor or retard their function. The pancreas undergoes extensive changes in the quantity and presumably also in the quality of its blood supply with each digestive cycle. As the activity of the acinar cells may be assumed to be favored by the more abundant and probably more highly oxygenated blood stream during digestion, it is possible to conceive that the islands likewise are aided by this means to furnish an increased quantity of the internal secretion which is necessary for the assimilation of the food after its absorption. On the other hand it might be imagined that the island function is favored by a slower flow of blood of more venous character, that the two pancreatic functions to some extent alternate, the islands resting while the acini are working at their maximum, and vice versa, or again that the formation of the hormone

within the island cells may be favored by one circulatory phase and its discharge from the cells may be promoted by another circulatory phase. Even granting the absence of a specific control of the island function by secretory nerves, it might be possible for a pure vasomotor disorder to influence the occurrence of diabetes, either by a vasoconstriction rendering the blood flow through the islands inadequate, or by a vasodilatation driving the cells to overfunction until they are exhausted. Such a disorder might either leave no anatomic signs of its existence or might lead to visible degeneration.

Some experiments were therefore undertaken with reducing and increasing the vascular supply of pancreas remnants in dogs.

I. REDUCTION OF VASCULAR SUPPLY

Dog B2-48. — Female; mongrel; yellow and white; age 4 years; good condition; weight 14.75 kilos. March 19, 1914, removal of pancreatic tissue weighing 22.5 gm., leaving remnant about main duct estimated at 4.7 gm. (1/6). The vessels on both sides of the remnant were ligated, leaving only one arterial and one venous branch open, which seemed the minimum circulation that would prevent necrosis. Glycosuria was absent at first on bread and soup diet, and after March 30 with addition of 200 to 300 gm. of glucose daily. This glucose feeding was prolonged to try the possibility of any delayed failure of function, but the tolerance was maintained precisely as when the blood vessels are left undisturbed. Death occurred unexpectedly on May 9, when the dog was apparently thriving, and without discoverable cause. The pancreas remnant weighed 6.8 gm., so that it had been able actually to hypertrophy. Its artery and vein had apparently enlarged so as to constitute an adequate blood supply. Both acini and islands were normal microscopically. The ligation of vessels had apparently had not the slightest influence upon the course of the experiment.

Dog D4-84. — Female; Newfoundland; age 5 years; good condition; weight 21.25 kilos. April 19, 1917, removal of pancreatic tissue weighing 32.6 gm., leaving remnant estimated at 5.7 gm. (1/7). This remnant was formed from the uncinate process, most of this process being carefully dissected away so as to leave a somewhat isolated piece communicating with the main duct and receiving the entire blood supply of this end of the pancreas, namely several branches passing into it from the trunks along the duodenum, together with the inferior pancreaticoduodenal vessels (which were very large in this case) from the other side. This arrangement was originally planned as convenient for the method of vascular stasis described in paper 6 of this series. The blood supply was clamped on June 12 for 15 minutes and

on June 27 for 65 minutes with the result of only transitory glycosuria. The dog remained able to thrive on bread and soup with 200 gm. of glucose daily without glycosuria. The question arose whether a permanent interference with the vascular supply would be more effective than the temporary stasis.

July 20, operation showed the pancreas remnant normal in appearance and free from adhesions, with its original vascular supply intact. The inferior pancreaticoduodenal vessels were cut between ligatures, also the large vascular trunks along the duodenum just cephalad from the pancreas remnant. The duodenal vessels on the other side of (caudad from) the pancreas remnant were thus left entirely without pulsation. The venous drainage was abundant, but there was a question whether the collateral arterial circulation would suffice to prevent necrosis in the pancreas or duodenum.

Slight glycosuria occurred in the hours following operation, then ceased and remained absent on bread and soup diet with addition of 300 gm. of glucose daily. Aug. 3, the pancreas remnant was found unchanged in appearance and without adhesions to furnish any appreciable blood supply. The single pedicle of vessels (together with the duct) was clamped for 70 minutes, with the result that glycosuria could again be produced by the glucose diets for only a few days.

Aug. 31, the pancreatic vessels were clamped for 95 minutes, with the result that heavy glycosuria occurred on bread diet with 100 gm. of glucose and passed on into permanent diabetes.

In this experiment the sudden great reduction of the vascular (especially arterial) supply of the remnant had no perceptible effect either in producing immediate diabetes or in facilitating its production by the method of temporary asphyxia.

Dog E5-52.—Female; mongrel; brindle; age 3 years; good condition; weight 20 kilos. May 24, 1917, removal of splenic process and body of pancreas, weighing 24.5 gm., leaving uncinate process, estimated at approximately one-third of the gland.

The pancreatic vessels were clamped for 40 minutes on June 15, 40 minutes on June 27, and 65 minutes on July 12, with the result of transitory glycosuria on bread and glucose diets each time.

July 20, all discoverable veins to the pancreas remnant were cut between ligatures, leaving the arteries intact. This operation could be done accurately because the remnant lay as a nearly isolated mass in the mesentery. The only exit left for blood was through tiny mesenteric venules. No glycosuria ensued on bread and soup diet with addition of glucose up to 200 gm. daily.

Aug. 3, the pancreas remnant was found slightly adherent to adjacent peritoneum where the veins had been divided, but there was no appreciable hemorrhage when the adhesions were broken. The vessels were clamped for 85 minutes on this day, for 90 minutes on Aug. 24, and for 1½ hours on Sept. 7, diabetes resulting after the last operation. Small specimens of tissue taken at these times showed nothing unusual, in particular no hydropic changes. At autopsy on Nov. 30 the pancreas remnant weighed 11.4 gm., and showed the usual extreme

hydropic degeneration corresponding to advanced diabetes but nothing attributable to the occlusion of veins.

Several experiments of each of the above types were performed with similar results. Also trials were made of leaving a pancreas remnant with a single vascular pedicle, which was surrounded by a heavy ligature with its ends protruding outside the abdomen, so that exulceration of the ligature meant obliteration of the vessels. This plan encountered difficulties in adhesions and infections, and was obviously inferior to the method of isolated grafts described in the preceding paper. Also a number of experiments were performed in which too extensive ligation of the arterial supply led merely to quick death from necrosis of the pancreas remnant. As far as could be determined by these experiments, no middle ground exists with vascular ligations and only one of two extreme results can follow; either acute necrosis causes death as mentioned, or with any degree of interference short of this the animal merely survives without symptoms and without any increased tendency to diabetes.

II. INCREASE OF ARTERIAL SUPPLY

Colleagues skilled in vascular suture assisted in the attempt to anastomose the small artery supplying a pancreas remnant with some large artery, such as the splenic, so as to turn the force of a large arterial current directly upon the remnant. From what is known of collateral circulation after ligation of large trunks, such a procedure should result in marked enlargement of the pancreatic arteries and a correspondingly richer arterial circulation. The failure of these attempts compelled recourse to less drastic methods.

Numerous efforts were made to form a suitable remnant in the splenic process of the pancreas, so that ligation of the splenic artery might throw a greater current into its pancreatic branch. But when a remnant small enough to permit diabetes is left around the principal pancreatic branch of the splenic artery (corresponding to the pancreatica magna in man) a long stretch of bare duct must be left to drain it, and it was found that the pancreatic duct will not exist in this naked state but becomes obliterated. In other experiments the duct was removed along with the pancreatic tissue, the

remnant of the splenic process was anchored to the duodenum in the region of the pancreatic duct, and the duct issuing from the remnant was anastomosed with the stump of the main duct, but failure always resulted from obliteration or some other accident.

There are wide variations in the vascular supply of the uncinate process of the pancreas in different dogs, and by keeping watch through a series of operations for an animal with the desired arrangement of vessels, a limited range of experimentation is feasible upon the circulation of a remnant in this part of the gland, as illustrated in the following example.

Dog D4-96. — Male; long-haired yellow mongrel; age 3 years; medium nutrition; weight 11.6 kilos. At operation on Feb. 14, 1917, the inferior pancreaticoduodenal vessels were found to be very large and to pass almost exclusively to the duodenum, giving off only a small side-branch to the margin of the uncinate process not far from the duodenum. The uncinate process was unusually small, and was nourished chiefly by anastomotic vessels from the body of the gland and the duodenum. By the removal of 3.4 gm. of tissue, a remnant estimated at 1.8 gm. was left near the duodenum, draining into it through a short segment of naked duct, and supplied only by the small side branch of the inferior pancreaticoduodenal vessels, all other vessels being ligated.

March 23, this remnant was found normal in appearance, with the circulation and duct drainage as arranged, and free from adhesions. All the rest of the pancreas, weighing 19 gm., was removed. The remnant was thus between 1/13 and 1/14 of the pancreas.

Heavy glycosuria ensued on a single day of bread diet, but was checked immediately by fasting. The tolerance for protein was then tested by beginning with 100 gm. of beef lung daily and increasing by 100 gm. per day. In 2 successive series, 300 gm. of the lung was tolerated but 400 gm. caused glycosuria. The dog then remained on 300 gm. lung and 100 gm. suet daily without glycosuria.

April 12, the pancreas remnant was found normal in appearance, free from adhesions, and possibly slightly hypertrophic. Its measurements taken as accurately as possibly with compasses were 2.5 x 1.5 x 1 cm. The large stem of inferior pancreaticoduodenal vessels was ligated just distal to its small pancreatic branch, and in consequence the tiny artery of this branch was seen to swell and begin pulsation which had not been visible before.

The previous diet tests were immediately repeated. Glycosuria remained absent with 300 gm. and also with 400 gm. of lung, but with 500 gm. became heavy and required 2 days of fasting to abolish it. On the next test traces of glycosuria appeared on 300 gm. of lung. After fasting and lower diet, the dog became able by May 9 to tolerate

the former diet of 300 gm. lung and 100 gm. suet. A ration of 400 gm. lung and 100 gm. suet was tolerated from May 11 to 16, but glycosuria then necessitated lower diets, in which the protein allowance did not rise above 300 gm. of lung. Also, in consequence of so much fasting and low diet, the weight gradually fell to 8 kilos, though the dog remained in good spirits. The fall in weight should of itself have raised the tolerance, but its influence was neutralized by the frequent repetitions of slight glycosuria. Altogether, however, it was sufficiently evident that the assimilation had not been improved by the attempted increase of the pancreatic circulation.

June 6, the vascular bundle to the pancreas remnant was found distinctly enlarged, visible and palpable pulsation being present in the artery and the vein also appearing wider in caliber than before. The remnant itself was slightly hypertrophied, its measurements now being 3.2x2.1x1.2 cm. In preparation for testing the opposite kind of circulatory change, the duodenum was anchored against the abdominal wall and the pancreas remnant was embedded in the tissues of the wall, retaining its vascular pedicle at one end and its duct at the other. Also a tiny lobule weighing less than 0.1 gm. was clipped off as a specimen. Microscopically this was free from fibrosis, and consisted of large acini crammed full of zymogen leaving only a narrow rim of basophilic substance. A few small islands were composed of cells which were rather pale but not vacuolated, but in one larger island one distinctly vacuolated cell was found. This degree of hydropic change was approximately what should be expected with the numerous recurrences of slight glycosuria.

The former feeding tests were repeated, and 300 gm. lung with 100 gm. suet was slightly above the tolerance. The undernutrition resulted in a fall of weight to 7.25 kilos by June 27. As the dog tired of fat and began to refuse it, the weight fell lower while the protein tolerance rose, so that by July 12 the weight was 6.5 kilos and 800 gm. of lung was eaten daily for a week without glycosuria. The plasma sugar also was normal (0.118%). Part of this change was undoubtedly mere cachexia and not actual improvement.

July 12, operation showed that the vascular pedicle of the pancreas remnant had atrophied to a fibrous cord which did not bleed when cut. No vessels accompanied the duct, so the entire nutrition of the graft had evidently been obtained from its new environment. The dog was too weak to survive the operation, and died on the evening of July 13.

At autopsy the pancreatic duct was found patent, and the graft, which was composed of soft and normal appearing tissue, weighed 2.4 gm. The actual hypertrophy may have been somewhat greater than indicated by this figure, for the weight of the remnant may have diminished somewhat in the general wasting of tissues. Microscopically only a trivial marginal fibrosis was present. The acini were normal though irregular in zymogen content. Islands on the whole were scarce and small but no vacuolation could be discovered in them.

Though hypertrophy of the pancreas remnant occurred in

this experiment, there is no ground for attributing it to the increase of circulation, for equal or greater hypertrophy is practically the rule after any partial pancreatectomy, and there was an impression that hypertrophy had begun before the alteration of circulation had been undertaken. Also the circulatory change had no appreciable effect upon the tolerance or the causation or prevention of vacuolation in the islands. The subsequent transplantation to the abdominal wall and obliteration of the vascular pedicle also failed to produce any perceptible effect in the opposite direction.

Another question kept in view has been that of the hemorrhages in the islands of Langerhans occasionally encountered in both diabetic and non-diabetic human necropsies. These have never been found in any animals of the entire series — not with increased or decreased circulation, or venous stasis, or any infection or intoxication or any of the numerous acute or chronic causes of death observed, or with prolonged agonal states, or with convulsions, or with rough handling of the tissue at autopsy. The numerous hemorrhages produced by trauma or temporary asphyxia of the pancreas remnant, as described in the preceding paper, have been found most often in the connective tissue septa, much less frequently among the acini, but never inside the islands as in human pathology. A special fragility of the island capillaries therefore seems excluded, at least in dogs and the other species studied, and the cause of the hemorrhages in question remains unexplained.

SUMMARY AND CONCLUSION

By operative methods it was possible to reduce the arterial supply or the venous drainage of pancreas remnants to a considerable extent, or to increase the arterial circulation to at least a slight extent. All these circulatory changes failed to alter the assimilative function or the pancreatic structure in any way. In particular, they failed to produce vacuolation, "atrophy", fibrosis or any other specific island changes. The experiments therefore throw no light upon the pathology of diabetes and afford no support for any circulatory or vasomotor theory of the etiology.

EXPERIMENTS ON CARBOHYDRATE METABOLISM AND DIABETES¹.

4. DEXTROSE-NITROGEN RATIOS IN PARTIALLY DEPANCREATIZED DOGS.

BY FREDERICK M. ALLEN AND MARY B. WISHART

*From the Hospital of the Rockefeller Institute for Medical Research,
New York.*

Minkowski² fixed the D:N ratio of totally depancreatized dogs at 2.8:1. There was some debate among the early investigators as to whether every completely depancreatized dog must show this full ratio and whether a lower ratio is proof of an incomplete extirpation. Minkowski acknowledged that the urine may become actually sugar-free for a short time before death, and it is now generally recognized that infection, weakness or unknown metabolic disturbances may sometimes lower the ratio or even prevent glycosuria³.

Langfeldt⁴ has reported "total" D:N ratios in dogs with the Sandmeyer type of diabetes, namely those in which diabetes followed the atrophy of a pancreas remnant left isolated from duct communications. Helly⁵ studied the glycogen storage of dogs which were made diabetic by removal of sufficient portions of the pancreas, leaving the remnant communicating with the patent duct so as to prevent atrophy and maintain good digestion. He found that such animals maintain, at least for long periods, glycogen deposits which are much higher than those of totally depancreatized dogs.

One of the present writers⁶ was the first to report the complete elimination of administered doses of sugar by animals of this type and also to give figures showing "total" D:N ratios in partially depancreatized animals. The best example is that of dog No. 64. The ratios were not calculated at that time, because attention was centered upon another subject, but the figures given for sugar and nitrogen in the table beginning on page 357 of the reference afford a basis for the reckoning shown in Table I.

TABLE I.

Dog 64

Date 1910	Urine				Diet
	Vol. cc.	Glucose, gm.	Total-N, gm.	D:N ratio	
July 6	725	30.64	9.49	3.24	350gm. meat.
" 7	1160	63.04	13.77	2.74	" " 9:00 A. M. given subcut. 25gm. glucose in 5% solution.
" 8	790	20.86	11.58	1.81	350gm. meat.
" 9	730	29.53	11.10	2.66	" "
" 10	630	15.84	8.77	1.81	" "
" 11	550	34.44	10.62	3.24	" "
" 12	625	36.98	11.79	3.14	" " 9:00 A. M. given a subcut. injection of 500cc. of 0.85% saline.
" 13	805	42.09	12.27	3.44	500gm. meat.
" 14	1152	48.36	13.30	3.64	" "
				2.86	average ratio for 9 days.
" 20	885	52.09	13.38	3.92	500gm. beef.
" 21	855	38.28	13.28	2.88	" "
" 22	1315	67.59	14.29	2.35	" " . Given subcut. 34gm. glucose in 80% solution
" 23	1108	52.33	17.10	3.06	500gm. beef.
" 24	1205	51.98	16.48	3.15	" "
" 25	1015	56.58	13.52	4.26	" "
" 26	560	25.37	9.84	2.59	" "
" 27	955	52.71	13.94	2.28	" " . Given subcut. 21gm. Levulose.
" 28	1115	44.07	18.61	2.37	500gm. beef.
" 29	860	43.89	17.42	2.52	" "
" 30	480	26.98	11.48	2.35	" "
" 31	580	36.60	13.65	2.68	" "
Aug. 1	555	40.17	12.60	3.19	" "
" 2	660	31.29	13.26	2.36	" "
				2.70	average ratio for 14 days.

Subtracting the quantities of administered glucose or levulose, it is seen that the D:N quotients for a 9-day period averaged 2.86, and for a subsequent 14-day period averaged 2.7. The daily ratios are more variable than in the usual totally depancreatized animal, perhaps in relation to the greater power of glycogen storage described by Helly. No totally depancreatized dog could maintain such maximal ratios for such a period as July 6 to August 2, because of the fatal cachexia. This dog maintained excellent spirits and vigor and died on

August 19 as the result of an operation on Aug. 17 (page 965 of reference). Diabetes had originally been produced in this animal on June 2 by the removal of 22.2 gm. of pancreatic tissue, leaving a remnant of 2 gm. At autopsy this remnant was found not shrunken and only slightly fibrosed. Microscopically the acini were normal and full of zymogen, but no definite islands could be found. The loss of islands had evidently been due to the usual hydropic degeneration, as the diabetes had been of very mild grade at the outset.

Subsequent experience has furnished a number of other observations of this kind, but has also proved that the D:N ratios of partially depancreatized dogs are not necessarily maximal, even when the diabetes is of fatal severity. Two typical examples are shown in Tables II and III.

Table II pertains to a dog which weighed 13.4 kgm. at the first operation on April 16, 1915, when the pancreas was estimated at approximately 30 gm. After several successive removals of pancreatic tissue, glycosuria began on carbohydrate diet July 21 and continued on carbohydrate-free diet after Aug. 9.

TABLE II.

Date 1915	Weight, kgm.	Urine				Diet
		Vol. cc.	Glucose, gm.	Total-N, gm.	D:N ratio	
Sept. 5	8.76	1500	21.75	20.89	1.04	600gm. raw pancreas 600gm. cooked lung 100gm. suet, bone meal.
" 6	—	803	36.50	21.75	1.60	As above.
" 7	—	665	31.70	16.25	1.95	500gm. raw pancreas 600gm. lung
" 8	—	1050	45.60	22.10	2.06	As above.
" 9	8.88	800	30.80	17.55	1.75	" "
" 10	—	980	26.50	15.00	1.76	" "
" 11	8.60	955	29.40	23.70	1.24	" "
" 12	—	600	21.80	14.20	1.54	" "
" 13	8.53	780	27.30	14.00	1.95	" "

The dog was killed on Sept. 14 when at the point of death from typical diabetic cachexia. At autopsy the pancreas remnant weighed 1.2 gm. Microscopically it was slightly fibrosed; the acini were normal, and islands were represented only by tiny groups of alpha cells and rare, maximally degenerated beta cells. It will be seen from the table that the D:N quotients averaged below 2.

TABLE III

Date 1915	Weight, kgm	Urine				Diet
		Vol. cc.	Glucose, gm.	Total-N, gm.	D:N ratio	
Feb. 5	14.90	986	6.66	5.40	1.22	200gm. lung, 400gm. suet.
" 6	—	980	9.80	7.60	1.29	As above
" 7	—	Lost				" "
" 8	—	808	10.67	5.98	1.72	" "
" 9	14.51	Lost				Fasting
" 10	14.20	1160	3.01	3.82	0.79	"
" 11	14.08	724	1.70	2.90	0.58	"
Ap. 5	9.30	290	5.10	2.26	2.26	Fasting
" 6	9.11	140	neg.	1.10	—	"
" 7	8.97	230	"	2.12	—	200gm. lard.

Table III deals with a dog weighing 15 kgm., which was made mildly diabetic by removal of 32.2 gm. of pancreatic tissue on Nov. 10, 1914, leaving a remnant estimated at 4.7 gm. Glycosuria was kept almost constantly absent on regulated diets, while the dog was used for a variety of feeding experiments which involved occasional hyperglycemia or slight temporary sugar excretion. The assimilation was thus gradually impaired (as in human cases under similar treatment) so that after Jan. 25, 1916, glycosuria was continuous on a diet of 200 gm. lung and 400 gm. suet, though the dog still weighed 15 kgm. From this point the downward progress was rapid. The table shows that on the diet mentioned the D:N quotient in early February ranged from 1.22 to 1.72, and with 3 days of fasting fell to 0.58.

With continuance of liberal carbohydrate-free diets there was continued loss of weight and strength. Though D/N quotients were not obtained during this time, it is possible that they may have been maximal. Fasting was begun April 1, and by April 5 the quotient was still 2.26. Contrary to the general rule with dogs of this type, glycosuria then ceased completely with extreme prostration of strength. The cessation was due to failure of the renal function rather than to control of the diabetes, for the plasma sugar on April 7 was still 0.323%.

The dog was chloroformed at the conclusion of the observations of April 7, when near death from cachexia. The pancreas remnant, weighing 4.7 gm., showed the usual normal acini together with recognizable remains of islands. The alpha cells were well preserved as usual, while the considerable number of beta cells present were all maximally vacuolated.

The record of dog No. B2-30, published in a previous paper⁷, affords an example of hopelessly severe diabetes with low D:N ratios. The animal fasted from Feb. 2 to March 20, 1914. The D/N quotients ranged from 0.22 to 1.63. Glycosuria was absent after March 8, but hyperglycemia could not be abolished. The attempt was then made to feed

minimal quantities of protein and fat and gradually build up a diet, but tolerance for any living ration could not be developed, and the moribund animal had to be chloroformed on April 24. The pancreas remnant, weighing 3.9 gm., was normal to gross and microscopic examination except for the nearly total absence of islands, which were reduced to small groups of alpha cells and rare degenerated beta cells.

It might seem an attractive hypothesis that maximal D:N ratios begin when all the beta cells of the pancreatic islands are lost, and that the lower ratios up to this time are proof of the persistence of some function in the remaining beta cells even when these are maximally vacuolated. A number of experiments, however, exclude this assumption by showing low D:N ratios when the beta cells have disappeared to the degree seen in the above dog or even more completely. In addition, there are instances of greater clinical severity of diabetes in the presence of larger numbers of vacuolated beta cells.

As an example may be cited the record of dog No. B2-01, previously published⁸. Very mild diabetes resulted from an operation on Aug. 31, 1916. The high tolerance gradually declined, especially in consequence of high calory, carbohydrate-free diets which kept the animal too fat. After August 1919, fasting and very low diets had to be used to check glycosuria, and hyperglycemia persisted nevertheless. The diabetes was never allowed to go unchecked, however, and when no diet could be tolerated any longer, the dog was fasted from Oct. 16 to death on Nov. 15, 1919, in a vain attempt to stop the glycosuria. Sugar was present even in the autopsy urine. The D/N quotients, however, were low during fasting (0.21 to 0.68). On a single day (Nov. 8) when only 100 gm. of lean beef was fed, the quotient jumped suddenly to 2.1. This result, however, followed a four day period in which the urine was sugar-free merely from renal impermeability, the plasma sugar being 0.322%, so the protein food may have acted largely as a diuretic. There was no perceptible influence of two days of fat feeding during this period.

At autopsy the pancreas remnant weighed 6 gm. The acini were normal as usual. Islands, though scarce and small, in addition to the usual few alpha cells contained considerable numbers of maximally vacuolated beta cells.

Totally depancreatized dogs are usually plunged suddenly from a state of good nutrition into the severest diabetes, while animals possessing a pancreas remnant of any considerable size reach the severest stage, characterized by absence of beta cells, only through an extended period of downward progress which is generally attended with emaciation and loss of strength. If a normal dog were to be subjected to fasting or

undernutrition, and then totally depancreatized after reaching a state comparable to that of the most cachetic partially depancreatized dogs, it would not be surprising if maximal D:N ratios failed to develop. By suitable feeding, however, it is possible to damage the assimilative power progressively while the animal is kept at full weight or even fattened. For example, the above dog No. B2-01 at the outset of the final fasting period still possessed her original normal weight of 14 kgm.

A similar illustration is given by the previously published record⁹ of dog No. B2-80. This animal had been fattened while diabetic so as to bring on fatal acidosis. During the 3 days preceding death in coma the D/N quotients were 2.07, 2.50 and 1.06. The autopsy urine was heavy with sugar and ketones, as in human cases. Cachexia or weakness in the ordinary sense was never present. In addition, the pancreas remnant afforded one of the most perfect examples of absence of beta cells as far as the most thorough search could determine¹⁰. All these factors, the high nutritive level, the severe acidosis, and the extreme loss of beta cells failed to maintain maximal D:N values during fasting.

It must be recognized, however, that such experiments replace one abnormality of nutrition by another. The diet, though high, is one-sided. There is a prolonged impairment of carbohydrate utilization, while at the same time the body is crammed with fat, which must monopolize the metabolism to a high degree. It is possible that this condition may affect the D:N ratio, and the suggestion that the lower ratios of partially depancreatized dogs during fasting may be explained by their special nutritive state is therefore not entirely excluded.

In this discussion of the effects of malnutrition, no valid comparison can be made with phlorizinized dogs, whose glycosuria seems to depend chiefly upon the intact state of the kidneys and continues during profound cachexia and after removal of the liver, adrenals or other viscera, which abolish the glycosuria of depancreatized dogs by abolishing hyperglycemia.

TABLE IV.
Dog E5-98

Date 1917	Weight, kgm.	Urine				Diet
		Vol. cc.	Glucose, gm.	Total-N, gm.	D:N ratio	
Sept. 30	17.75	1135	40.80	8.88	4.60	Not fed.
Oct. 1	—	340	14.96	4.32	3.40	200gm. lung.
" 2	—	830	47.70	17.60	2.71	400gm. "
" 3	—	448	39.90	11.75	3.39	600gm. "
" 4	—	978	93.30	18.40	5.05	800gm. "
" 5	—	504	43.40	11.46	3.79	" "
" 6	—	895	57.40	22.84	2.51	" "
" 7	—	950	56.50	24.96	2.17	" "
" 8	—	1490	112.80	31.92	3.53	" "
" 9	—	755	58.20	18.32	3.17	" "
" 10	13.50	960	56.00	23.60	2.37	" "
" 11	—	940	52.10	20.48	2.57	" "
" 12	—	675	52.20	11.08	4.72	" "
" 13	—	1280	84.80	36.40	2.33	" "
" 14	—	700	43.50	—	—	" "
" 15	—	494	18.70	17.00	1.10	" "
" 16	—	290	0.84	12.30	—	" "
" 17	—	345	Faint	15.20	—	" "
" 18	—	760	20.60	25.76	0.80	" "
" 19	10.70	400	10.44	—	—	" "

"Total" D:N ratios are uncommon immediately after partial pancreatectomy, even when the remnant is very small. Dog E5-98, whose record is shown in Table IV, was a male mongrel, aged 4 years, in excellent nutrition. Sept 28, 1917, 34 gm. of pancreatic tissue was removed, leaving a remnant estimated at 1.3 gm. (1/27). The first food was given on Oct. 1. The high D/N quotients of Sept. 30 and Oct. 1 are evidently explainable by sweeping out of body glycogen. The quotients for the next 12 days average 3.20. This high figure is perhaps to some extent similarly explained by glycogen. For example, with the increase of diet to 800 gm. of lung on Oct. 4 there was evidently some sudden stimulus to sugar elimination, which apparently carried out glycogen retained from the time before the operation. After Oct. 14 the quotients fell sharply with failure of strength, though glycosuria increased at the end. On Oct. 19 the dog ate his full diet as usual and died within a few hours thereafter, with sugar-rich urine in the bladder. The length of life was thus not much longer than that of some totally depancreatized dogs.

The pancreas remnant weighed 2.21 gm. Microscopically it was free from fibrosis, and the acini normal and full of zymogen. Islands were fairly abundant, and though vacuolation was marked in all beta cells, it had not yet reached its maximal stage. This observation casts doubt on the functional value of cells in the widely vacuolated condition, though the very small size of the remnant must be considered. In particular, it shows that maximal D:N ratios may exist in some isolated

cases with a larger pancreas remnant than should be overlooked in any careful operation, and therefore that such ratios are not an infallible proof of a total pancreatectomy.

Table V is the record of a dog which for 2 months had possessed no pancreatic tissue except a subcutaneous graft secreting through its duct transplanted to the skin. Diabetes had been mild at first but had progressed to the severe stage in which glycosuria was continuously heavy on carbohydrate-free diet notwithstanding the poor digestion and resultant emaciation. The dog was killed on Sept. 22 when too weak to stand. Though the D:N ratios resembled those of a totally depancreatized dog, the duration of life was greater, a more advanced state of emaciation was reached before death, and the general spirits and vigor were far better maintained. The better general strength may be a reason for the apparently better digestion of such animals as compared with totally depancreatized animals. Though totally depancreatized dogs often lose appetite at the end, this dog ate his diet to the last day, and this fact may explain the maintenance of the high D:N ratios to the end.

The pancreas graft at autopsy weighed 5.5 gm. Islands were fairly abundant, and all beta cells were maximally vacuolated. This experiment again raises the question whether these cells have any functional value in the final stage of their vacuolation. It mainly indicates, however, that the cachexia and early death of totally depancreatized dogs are not entirely explained by either the non-utilization of sugar or the absence of pancreatic juice from the intestine.

TABLE V.

Date 1915	Weight, kgm.	Urine				Diet
		Vol. cc.	Glucose, gm.	Total-N, gm.	D:N ratio	
Sept. 4	11.15	1755	46.50	15.70	2.96	500gm. pancreas 500gm. lung 200gm. suet.
" 5	—	1360	51.35	20.40	2.51	As above.
" 6	—	1635	43.00	18.17	2.37	500gm. pancreas 800gm. lung.
" 7	—	2030	75.10	36.26	2.08	As above.
" 8	10.55	1460	57.50	20.90	2.75	" "
" 9	—	1560	74.30	25.70	2.89	" "
" 10	10.78	2930	93.15	29.10	3.20	" "
" 11	—	2300	49.05	20.43	2.40	" "
" 12	—	3080	91.00	33.45	2.72	" "
" 13	9.73	1560	56.16	18.05	3.11	" "
" 14	—	1660	68.56	24.40	2.81	" "
" 15	—	1520	51.50	20.45	2.52	" "
" 16	9.48	2840	82.33	31.30	2.63	" "
" 17	—	1780	58.40	22.50	2.60	" "
" 18	—	1805	54.54	18.55	2.94	" "
" 19	8.88	1910	48.25	19.85	2.43	" "
" 20	—	2020	54.96	16.76	3.28	" "
" 21	8.60	2135	65.20	23.70	2.75	" "
				Average	2.72	

DISCUSSION AND CONCLUSIONS.

The above observations, together with those quoted from the literature, seem to warrant the following conclusions or suggestions, particularly with reference to the question of a plurality of internal secretions of the pancreas and the separate functions of the beta cells and of the elements which remain after the beta cells have degenerated.

1. Total pancreatectomy does not invariably give rise to a permanent "total" D:N ratio of 2.8:1. The meaning of the lower ratios sometimes observed with fasting, cachexia or obscure conditions is not understood. The presumption may be warranted that a totally depancreatized animal with the lower ratio is as completely diabetic as one with the maximal ratio, and it seems improbable that the missing glucose or glucogenic material is disposed of in any normal or beneficial manner.

2. Incompletely depancreatized animals sometimes show D:N ratios lower than 2.8:1. Sometimes, however, they display the "total" ratio, either immediately after operation when the pancreatic remnant is extremely small, or more commonly in the later stages of prolonged diabetes. The D:N ratio, therefore, is not an infallible test for deciding whether the entire pancreas has been removed.

3. Diabetes of fatal severity may exist even when the D:N ratio is rather low. In one grade of case, glycosuria may be stopped by fasting but no tolerance can ever be attained for a sufficient diet to support life. In a more severe grade, the glycosuria resists fasting, and after death from starvation sugar is found in the autopsy urine. Even in these extreme cases, however, the writers have never yet observed "total" D:N ratios maintained throughout any long period of fasting in partially depancreatized animals. On the other hand, if any animal shows the maximal ratio at any time, experience indicates that a fatal outcome is inevitable and attempts at treatment are hopeless. This difference from the experience with human cases may be explained by the fact that in animals the diabetes rests solely upon an organic deficiency of the pancreas and not in any degree upon a functional derangement.

4. The microscopic studies described in Series III confirm

those of Homans in relating carbohydrate metabolism to the beta cells of the pancreatic islands. Animals which have lost all discoverable beta cells may still show submaximal D:N ratios, as do some totally depancreatized animals. On the other hand, no exception has yet been found to the rule that when any partially depancreatized animal shows "total" D:N ratios, the beta cells have undergone complete vacuolation or degeneration.

5. The differences which ordinarily exist between totally and partially depancreatized animals, even when both show the same D:N ratio, may be classified as follows:

(a) The loss of both sugar and nitrogen by totally depancreatized animals is higher than that of partially depancreatized animals. Such a general statement is risky because of modifying conditions; for example, the former animals are plunged suddenly from a state of normal nutrition into the severest diabetes, while the latter animals generally reach the severest stage only after a protracted course of emaciation and asthenia; also, in fasting tests the partially depancreatized animals are apt (perhaps for this same reason) to show a fall of their D:N ratios much more readily than totally depancreatized animals. It appears probable, nevertheless, that a higher sugar and nitrogen excretion is typical of the totally depancreatized animals.

(b) The total basal metabolism is probably higher after total than after partial pancreatectomy, perhaps partly in consequence of the greater protein breakdown, but perhaps also because of a general melting down of tissues from lack of the pancreatic secretion. This higher metabolism may be a further reason why the D:N ratios of totally depancreatized dogs are generally less reduced by fasting than those of partially depancreatized dogs. This entire statement is partly hypothetical, as it rests only upon the apparently more rapid wasting of totally as compared with partially depancreatized dogs. The basal metabolism of the latter type of animals with severe diabetes has never been measured, but experiments of this sort would be of interest for determining whether there is anything like the enormous increase observed in totally depancreatized dogs.

(c) A striking difference is found in the better spirits and muscular strength, the less severe cachexia and prostration,

and the far longer life of the partially as compared with the totally depancreatized dogs. This difference is not a mere result of those mentioned under (a) and (b). The totally depancreatized animal does not starve to death, for it generally dies possessed of much greater stores of both nitrogenous (muscular) and fatty tissue than partially depancreatized or normal animals which succumb to prolonged starvation. The death also is evidently not due to the mere loss of sugar, for by small doses of phlorizin a normal or partially depancreatized dog may be made to exhibit the same or even higher sugar excretion, yet may remain in fair condition when the totally depancreatized dog is dead. The same distinction holds with regard to wound healing; the wounds of partially depancreatized or phlorizinized dogs heal reasonably well, regardless of the degree of hyperglycemia, glycosuria or D:N ratios, while the power of healing or of resisting infection seems to be almost abolished by total pancreatectomy. The evident metabolic disorder has heretofore diverted attention from the more fatal endocrine deficiency.

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EXPERIMENTS ON CARBOHYDRATE METABOLISM AND DIABETES.

5. THE INFLUENCE OF GLUCOSE INGESTION ON DIURESIS AND BLOOD COMPOSITION IN NON-DIABETIC AND DIABETIC PERSONS.

BY JAMES W. SHERRILL AND HENRY J. JOHN.

From The Physiatrie Institute, Morristown, New Jersey.

The observations on the diuretic action of sugar up to 1913 were reviewed by Allen¹, who called attention to the contrast between the general belief concerning this action and the actual anti-diuretic effect demonstrated in his experiments. He showed that glucose given by stomach, subcutaneously or intraperitoneally markedly diminishes urine in the non-diabetic organism, regardless of the dosage, the concentration of solution, the degree of hyperglycemia or glycosuria, or other factors. Glucose administered in these same ways to diabetic animals produced polyuria. When large doses of glucose were injected intravenously, the urine was increased in both diabetic and non-diabetic animals. Various control experiments were performed in the attempt to find an explanation of these phenomena, but it was not possible to make parallel examinations of the blood and urine at that time.

The earlier work of Fisher and Wishart² had included hemoglobin estimations, and also mentioned red cells counts in some experiments. From this evidence they concluded that 50 gm. of glucose by stomach tube causes in dogs oliguria accompanied by hydremic plethora.

Mosenthal and Hiller³, using a method of weighing the total dried solids of the blood, failed to demonstrate any constant relations between diuresis, blood concentration and blood sugar in diabetic or non-diabetic persons, and concluded: "The body has a tendency to increase the water content of the blood as the blood sugar rises. There are, however, other factors, such as diuresis, which break in on this parallelism".

Ewing⁴, using intravenous injections and judging blood dilu-

tion by the hemoglobin and specific gravity, obtained results in accord with those of Fisher and Wishart. He observed also that diuresis may occur without change in the specific gravity of the blood, or may be absent when there is a distinct dilution of the blood.

Woodyatt⁵ and collaborators observed an anti-diuretic effect of small intravenous doses of glucose. Diuresis began later than glycosuria. Large intravenous injections produced polyuria in addition to glycosuria and withdrew water from the body so powerfully as to cause intense thirst and fever. Sansum⁶ accomplished rapid reductions of intra-ocular tension by this means. Haden⁷ recommended glucose for the reduction of intra-cranial pressure. In all this work, however, there is a lack of sufficient observations on the blood to establish the direct influence of glucose upon the kidney function.

This same statement applies to the studies of numerous writers upon glucose ingestion as a test of carbohydrate assimilation. Bailey⁸ followed the hemoglobin and red cell volume in parallel with the blood sugar. The changes were mostly slight, though in the direction of oliguria and hydremia with hyperglycemia. A regular rate of fluid intake was lacking in this work.

The present investigation was undertaken to throw light on this interesting and unsettled point of glucose diuresis, by means of parallel observations of the blood and urine after glucose ingestion by human subjects.

SELECTION OF CASES

The tests were performed upon 19 individuals, including 5 non-diabetics, 9 patients with mild and 5 with severe diabetes.

The 5 non-diabetic subjects comprised 2 normal persons, 1 patient with simple obesity and 2 with arterial hypertension, all having normal power of carbohydrate utilization according to blood sugar and other tests.

Of the 9 cases of mild diabetes, only one (No. 230) was in an active stage with glycosuria. 7 of the others showed glycosuria of 0.2 to 1.2% after ingestion of the glucose. 1 of these had arterial hypertension and slight hyperthyroidism complicating the diabetes. The remaining patient had sought treatment for arterial hypertension alone; diabetes was diagnosed only from the blood sugar curve and the slight glycosuria after taking 100 gm. of glucose.

Of the 5 cases of severe diabetes, 1 (No. 85) was of 5 years' duration but had been well treated from the outset and had normal urine and

blood at the time of the test. Case 187 had glycosuria but no acidosis at the time. The other three (Nos. 173, 219 and 283) represented the active stage of very severe diabetes, with heavy glycosuria and acidosis.

In addition, control tests with sodium chloride and water ingestion were performed upon a patient with diabetes of moderate severity.

PROCEDURE

Each test was begun soon after rising in the morning, and no food was taken during the experimental period. In order to avoid the possibilities of altered metabolic functions due to exercise or polyuria due to nervous influences, all remained as quiet as possible, either in bed or sitting in their rooms. The diuretic influence of water itself and of retained body fluids were factors considered, and with the exception of patient No. 219 all were free from perceptible edema.

There was first a preliminary period of 3 hours with a constant water intake of 200cc. per hour, for control purposes and for obtaining as nearly as possible a water equilibrium. In every instance, thirst was fully satisfied by this fluid supply and there was never any complaint of thirst before or after glucose ingestion.

Urine specimens were obtained hourly and a blood sample at the end of the period. The test dose of glucose (generally 100gm., but reduced to 25, 30, or 50gm. for some of the 'diabetic cases') was then drunk dissolved in 200cc. of water, followed by a bite or two of lemon if necessary for nausea. A blood sample was taken $\frac{1}{2}$ hour afterward; and at each hourly interval till the close of the test the bladder was emptied, a blood sample drawn, and 200cc. of water was drunk.

METHODS

Pure anhydrous glucose was used, thoroughly dissolved in advance to insure the best absorption. Blood was drawn with a needle, after only slight and brief stasis, from a vein of the forearm into a dry Luer syringe containing a few crystals of potassium oxalate. It was immediately divided into two parts, one being used for the whole blood analyses and the other promptly centrifugalized and the plasma removed. Urine was voided voluntarily in each instance.

Urinary sugar was determined qualitatively and quantitatively with Benedict's copper solutions. Whole blood was analyzed for urea by Van Slyke's modification of Marshall's urease method. Sugar was determined by Benedict's picric acid method, generally in the plasma, sometimes also in the whole blood for comparison. Chlorides were estimated in the plasma by the McLean method. Hemoglobin was estimated with the colorimeter, using Palmer's carbon monoxide method. Readings of red cell volumes were made in accurately graduated tubes centrifugalized at 3000 revolutions per minute for 20 minutes. Red cell counts were repeated several times and checked by both observers.

Case 8.—J. W. S. Table 1, Chart 1. June 7, 1920.

Male, 29, single, physician, American.

Healthy adult male. Physical examination negative. Previous chemical analyses of the blood normal.

Preliminary period: The urine output averaged 167cc. per hour for 2 hours on a water intake of 200cc. per hour. Erythrocyte count 4,500,000, red cell volume 45.7%. Plasma sugar 101mg., plasma chlorides 610mg. per 100cc. Hemoglobin 96%.

The plasma sugar curve was normal after taking 100gm. of glucose. The urinary output, which had averaged 167cc. per hour during the preliminary observation, dropped to 110cc. at the end of the 2-hour period. Diuresis of 340cc. occurred at the end of the 4th hour. Red cell volume decreased from 45.7%, before giving the glucose, to 40.7% at the end of the second hour period. Plasma chlorides likewise decreased from 610mg. to 530mg. per 100cc. Hemoglobin decreased from 96% to 92%. There was a doubtful rise in the red cell count.

Case 19.—L. C. Table 2, Chart 2. June 17, 1920.

Male, Italian-American, 23, single, technician.

Past and family history negative. Physical examination negative. Always ate abnormally large quantities of protein. Two casual blood urea examinations previous to test were slightly elevated, being 35mg. and 40mg. per 100cc.

Preliminary period: On a constant water intake of 200cc. per hour, the output was 70cc. for the first and 490cc. for the second hour. Blood urea 35mg. per 100cc., plasma sugar 124mg. per 100cc., plasma chlorides 610mg. per 100cc. R. B. C. 6,344,000. Red cell volume 47.3%. Hemoglobin 101%.

The administration of 100gm. of glucose produced an immediate hydremia, as evidenced by the rapid dilution of the chlorides to 588mg. per 100cc. and the fall in cell volume. The changes in the plasma sugar were normal. The highest concentration occurred 30 minutes after the ingestion of the glucose. Red cell counts showed no significant changes throughout the experiment. Hemoglobin bore no direct relation to the counts, as it steadily decreased from 101% to 89% at the end of the test. Blood urea was reduced by this day of partial fasting from 35mg. to 16mg. per 100cc. This substance was readily excreted by the kidneys, a total of 14.9gm. occurring in the urine during the 9 hour test. The concentration of the urine varied with the volume, as shown in Table 2.

The interval at which oliguria and diuresis occurred is typical of the normal reaction. Oliguria occurred during hyperglycemia, followed by diuresis when hyperglycemia disappeared.

Case 264.—E. A. R. Table 3, Chart 3. June 1, 1920.

Female, 18, single, American, school girl.

This patient's only complaint was obesity, with gradual increase in weight for past 8 years. Distribution of fat peculiar, practically all of it being deposited about the abdomen and thorax. Limbs are practically normal in size and well formed, fingers slender and tapering.

Physical examination otherwise negative. Two previous blood analyses showed normal chemical constituents.

Preliminary period: 200cc. of water per hour was given for three hours previous to the administration of glucose. Water retention in this case was remarkable, as the patient excreted only 36cc. in 3 hours. She also retained a large amount of fluid throughout the whole experiment. R. B. C. before giving the glucose were 4,450,000, hemoglobin 80%, R. C. V. 40.9%. Plasma sugar 87mg., plasma NaCl 600mg. per 100cc.

The plasma sugar curve after the ingestion of 100gm. of glucose showed very little increase. It rose from 87mg., before the administration of glucose, to 102mg. at the end of the half hour period, and to 103mg. at the end of the hour period; it then decreased rapidly to the low value of 79mg. During the rise in plasma sugar there was a fall of the red cell volume from 40.9% to 32%. Plasma chlorides also decreased from 600mg. to 590mg. There was no change in hemoglobin. The red cell count fell slightly.

Unlike the other four non-diabetic cases, the urine volume did not decrease during hyperglycemia. Water retention during the preliminary period may account for the absence of oliguria. Diuresis also failed to occur immediately upon cessation of hyperglycemia as in the normal and the mildly diabetic subjects.

Case 188. — G. C. S. Table 4, Chart 4. April 10, 1920.

Male, 35, American, married, minister.

With the exception of arterial hypertension, the past history and physical examination were negative. Blood pressures were usually 200 to 220mm. systolic, 110 to 130mm. diastolic.

The preliminary period was for one hour only. 200cc. of water was given by mouth. The urine output was 320cc. Plasma sugar 98mg., plasma chlorides 588mg. per 100cc. Red cell volume 44.6%, red cell count 6,300,000. Hemoglobin 106%.

The plasma sugar showed a normal curve after taking 100gm. of glucose. Although it increased to 204mg. at the end of the 30 minute period, it dropped rapidly to 116mg. per 100cc. at the end of the hour period. Oliguria of 32cc. occurred one hour after taking the glucose. At the end of the third hour, after the plasma sugar had fallen to normal, diuresis of 310cc. occurred. The specific gravity of the 32cc. specimen was 1014, while that of the 310cc. specimen dropped to 1003. Corpuscle volume was not reduced during hyperglycemia, but at the end of the second hour it had fallen to 42.8%, and returned to 46.0% two hours later. The hemoglobin fell from 106% to 102% during hyperglycemia. The red cell count decreased synchronously with the cell volume, from 6,300,000 when the volume was 44.6% at the beginning of the experiment to 5,490,000 when the volume fell to 42.8%.

Water retention with hydremia was produced in this case by the administration of glucose, as shown by the decrease in blood count, hemoglobin and red cell volume.

Case 207. — E. E. T. Table 5, Chart 5. May 10, 1920.

Male, 58, American, single, clerk.

Past history negative. No diabetes in family. Slightly obese. With the exception of a chronic simple glaucoma, physical examination was negative. Blood pressure 120/80.

Preliminary period: Given 200cc. water per hour. The urine output averaged 52cc. per hour. R. B. C. 4,800,000, hemoglobin 74%. Plasma chlorides 580mg. per 100cc. Plasma sugar 108mg. per 100cc.

100gm. of glucose produced hyperglycemia of 181mg. per 100cc. within 30 minute, and it was slow in returning to normal. Red cell volume remained practically unchanged until the third hour, when it fell to 34%. Red cell count decreased almost 1,000,000 at the end of the first hour. This case is similar to Case 8, as the decrease in cell volume did not occur at the 30 minute period, but was delayed until the plasma sugar had begun to decrease. Hemoglobin fell from 74% to 66% at the end of the 3rd hour.

As in the other normal cases, oliguria occurred during hyperglycemia. The patient was unable to void urine at the end of the first hour. For the second and third hours the output was only 66 and 44cc. respectively. The hourly urine volume rose to 295cc. after the plasma sugar had fallen to normal.

Case 201. — L. L. Chart 6, Table 6. March 27, 1920.

Male, Hebrew, 33, married, business man.

Glycosuria discovered during insurance examination 4 months ago. Always in good health. Physical examination negative.

Preliminary period: On a water intake of 200cc. per hour the urine output was 75cc. per hour for 2 hours. Plasma sugar 125mg. per 100cc., plasma NaCl 620mg. per 100cc. Red cell volume 46.7%, hemoglobin 80%.

Administration of 100gm. of glucose produced hydremia, accompanied by oliguria. The red cell volume fell from 46.7% to 40.5% during hyperglycemia, and returned to 48.3% after hyperglycemia disappeared. Hemoglobin also diminished as the red cell volume decreased. It fell from 80% to 72% during hyperglycemia and returned to 77% at the end of the test. Oliguria was present as the blood sugar rose. The output was only 65cc. when the plasma sugar was at its height. Diuresis occurred at the 2nd hour, the output being 310cc. The output exceeded the intake by 100cc. during the next three hours.

This case represents well the effect of the sudden ingestion of a large quantity of glucose upon the blood volume and urinary excretion in the mildly diabetic individual. The diuresis was unusual, as it continued for so long a period of time. Plasma chlorides diminished during hyperglycemia and returned promptly to normal at the end of the experiment.

Case 241. — H. J. D. Table 7, Chart 7. May 1, 1920.

Male, American, 37, married, salesman.

Case of mild diabetes associated with slight obesity. Influenza in December 1918. Diagnosis of diabetes made at that time. The carbo-

hydrate in the diet was restricted and sugar has not been found since. Physical examination negative.

Preliminary period: On a constant water intake of 200cc. the hourly output approximated 100cc. R. B. C. 5,700,000; hemoglobin 96%; red cell volume 44.6%; plasma chlorides 630mg. per 100cc.

100gm. of glucose was given by mouth. A second blood specimen taken 30 minutes later showed a sharp rise in plasma sugar to 239mg. per 100cc., with an accompanying increase in the red cells to 7,200,000, and an increase in the blood urea to 32mg. per 100cc. The plasma chlorides fell to 615mg. per 100cc., and the hemoglobin to 92%. The red cell volume showed no change.

At the end of the first hour period the plasma sugar had risen further to 309mg. per 100cc. The urine showed the marked anti-diuretic effect of the glucose. There was water retention for this period, the volume being only 30cc., with a sugar content of 0.48gm. The anti-diuretic effect was apparent until the 8th hour. Hemoglobin was further decreased to 84%, and the red cell volume to 42.1%. The maximum level of blood urea was 38mg. per 100cc., and that of the chlorides 660mg. per 100cc.

The plasma sugar gradually fell to 128mg. per 100cc. at the end of the sixth hour. During the period of hyperglycemia the urine output averaged 51cc. per hour. The output during the 8th and 9th hours reached 175 and 130cc. respectively. Diuresis occurred later in this case than in the majority of cases of mild diabetes here reported, in which it usually occurred at the 4th hour. The hemoglobin, which fell to 84% at the end of the second hour, gradually returned to the initial value of 95% at the 8th hour. The hemoglobin in this case was inversely proportional in amount to the blood sugar.

In this experiment the different tests of blood volume were discrepant; the red cell count indicated a concentration of the blood during hyperglycemia, while the hemoglobin indicated a dilution and the red cell volume remained almost stationary. The outstanding feature is that glycosuria as high as 2.86% was accompanied by marked oliguria.

Case 204. — L. B. G. Table 8, Chart 8. March 30, 1920.

Male, 34, Hebrew, married, physician.

Case of mild diabetes of 2 months duration. Physical examination negative except for slight obesity.

Before giving the glucose the blood findings were as follows: plasma sugar 120mg., blood urea 40mg., plasma chlorides 633mg. per 100cc. Red blood count 6,600,000, red cell volume 43.2%, hemoglobin 100%. With the exception of the slightly elevated blood urea and high plasma chlorides there was no evidence of renal impairment.

100gm. of glucose produced hydremia which outlasted the hyperglycemia. Plasma chlorides decreased during hyperglycemia and returned to the original figure upon its cessation. Red cell volume was reduced from 43% to 38%. Hemoglobin decreased from 100% to 91%. Synchronous with hydremia, water retention was shown by the

low urine volume. The urine output for one hour after glucose administration was 48cc., with 1.72% sugar. The urine volume increased to 245cc. after the hyperglycemia had diminished to 0.169%. With a further fall in blood sugar to normal, diuresis of 247 and 230cc. occurred for the 2 hours following. Red blood counts in this case showed a slight dilution from 6,600,000 to 6,000,000 during hyperglycemia and oliguria.

This case of mild diabetes shows the combination of hyperglycemia and glycosuria with oliguria, notwithstanding the presence of hydremia.

Case 224. — W. F. Table 9, Chart 9. April 24, 1920.

Male, 64, American, single.

Case of arterial hypertension with mild diabetes. Past and family histories negative. Headaches, dizziness, dyspnea, precordial distress and nocturia for past six years. One year ago hemorrhage into left eye. Never had glycosuria or other diabetic symptoms. Fairly well preserved man. Sclerosis of peripheral vessels. Heart markedly enlarged downward and outward. Systolic murmur at apex. B. P. on admission 240-120. No dyspnea or signs of decompensation at time of test. Wassermann negative.

The blood sugar in this case had formerly been found normal, but 100gm. of glucose by mouth produced hyperglycemia of over 0.200% and glycosuria of 0.4%. This is the only case in the series in which disagreeable symptoms were produced by the glucose. The patient barely escaped vomiting. It may be noted that there was a rapid rise in the blood sugar from 0.103% to 0.207% in 30 minutes after taking the glucose, but this dropped to 0.142% at the end of the hour period, which corresponded to the period of extreme nausea. The blood sugar rose to 0.193% one hour later, after the nausea had ceased. Delayed absorption may have been a factor in producing the low blood sugar during the nausea.

The anti-diuretic effect of the glucose is clearly shown. The urinary output for the two hours before taking it was 117 and 108cc. This fell to only 86cc. for the two hours following. Diuresis in this case was delayed until the 4th and 5th hours, when the output was 282cc. and 215cc. respectively. The red cell volumes bore an evident relation to the glycemia. With the hyperglycemia of 0.207% at the end of the half hour period there was water retention, with a fall in red cell volume from 50% to 36%. This was followed at the end of the hour period by a fall in blood sugar to 0.142% and a rise in corpuscle volume to 46%. Again with the rise in sugar at the two hour period to 0.193%, there was an accompanying fall in red cell volume to 40%. The hemoglobin and red cell counts bore no constant relation to the blood sugar in this case.

Here it must be assumed that the individual red corpuscles underwent unusual changes in size with the variation in blood sugar. According to the red cell counts, the blood was slightly diluted or at least not concentrated during the period of hyperglycemia, but oliguria was marked in this period nevertheless.

Case 263.—Table 10, Chart 10. June 3, 1920.

Male, 35, Hebrew, married, merchant.

Mild diabetes was discovered during a life insurance examination 9 months previously. Patient felt slightly exhausted after a day's work; no other symptoms. He had been on a carbohydrate-poor diet and the urine was free from sugar and acetone. Physical examination negative. 100gm. of glucose was given as a diagnostic test.

The results are typical of a very mild or incipient diabetes. The red cell volume fell, and the slight changes in the erythrocyte count were in the direction of a dilution of the blood during the period of hyperglycemia. The urine volume was 45cc. for the first hour with 0.2% glycosuria, and 40cc. for the second hour with 0.42% glycosuria. In the third hour, when glycosuria had ceased and the plasma sugar had fallen somewhat, the urine output rose to 147cc., and in the fourth hour, when the plasma sugar was presumably still lower, the urine volume was 370cc.

Case 259.—W. S. H. Table 11, Chart 11. May 25, 1920.

Female, 40, married, American Hebrew, housewife.

Case of mild diabetes. Father, two brothers, and an uncle have diabetes. Patient has had hyperthyroidism five years with occasional tachycardia and tremor. Glycosuria was discovered two months ago. There were no apparent symptoms of hyperthyroidism, and the urine was negative for sugar and albumin at time of this test. Physical examination negative with the exception of blood pressure 190 systolic, 95 diastolic.

Preliminary period: On a water intake of 200cc., the urine output was 112cc., 143cc., 305cc., and 270cc. per hour. R. B. C. 5,456,000; R. C. V. 39.5%. Plasma chloride 590mg., plasma sugar 170mg. per 100cc.

100gm. of glucose produced a rise in blood sugar typical of diabetes. During hyperglycemia the R. C. V. decreased from 39.5% to 37.4%, and gradually returned to 42% after the plasma sugar returned to normal. Plasma chloride fell from 590mgm. to 580mgm. per 100cc. There was no important change in the red counts.

In this case, in contrast to the usual water retention, the output greatly exceeded the intake for every period. It was at its lowest immediately following the ingestion of glucose, but was not as markedly reduced as in the other cases of mild diabetes and the normal subjects. The largest urine volume, however, was 380cc. at the 5th hour, when the plasma sugar had fallen to normal.

Case 233.—L. M. W. Table 12, Chart 12. April 20, 1920.

Male, 52, American, married, physician.

Mild diabetes of one year's standing. Onset gradual with weakness, malaise, polyuria, and polyphagia, and loss of 22 pounds. Physical examination negative at the time of this experiment. No glycosuria and no acetone. 100gm. of glucose produced hyperglycemia of 0.204% in 30 minutes, with gradual return to normal in 3 hours.

In contrast to the oliguria observed in the majority of the cases, there is in this case a parallelism of hyperglycemia and polyuria. The

highest urine volume, 275cc., occurred during the first hour, with glycosuria of 0.6%. At the end of the 2nd hour the plasma sugar had fallen to 0.120%, but there was still glycosuria of 0.6%, and the urine specimen of 180cc. was the second largest in this experiment. The blood volume showed little consistent change according to the different tests.

Case 196. — A. H. Table 13, Chart 13. June 8, 1920.

Male, 16, Hebrew, schoolboy.

Sister, mother and maternal aunt have diabetes. Two months ago sugar was reported in the urine. There have been no other symptoms of diabetes, except a few pimples on the neck 2 weeks previously. Physical examination negative.

Preliminary period: The urine output was 65cc. and 150cc. hourly for 2 hours preceding the administration of glucose, on the usual water intake of 200cc. per hour. Plasma sugar 118mg., plasma chlorides 610mg. per 100cc. R. B. C. 5,440,000. Hemoglobin 106%.

Ingestion of 100gm. glucose produced hyperglycemia for 2 hours, although glycosuria was absent. Plasma chlorides, corpuscle count and red cell volume decreased during hyperglycemia. There was oliguria during the hyperglycemia, and diuresis of 270 and 300cc. during the 3rd and 4th hours respectively.

Case 230. — I. J. B. Table 14, Chart 14. April 19, 1920.

Male, 20, married, Hebrew, business man.

Case of mild diabetes of acute onset and 2 months' standing. Mother died of diabetes. Patient had heavy glycosuria and symptoms of mild acidosis when test was performed.

Preliminary period: On a constant water intake of 200cc. per hour the urine output was only 26, 30 and 34cc. per hour. Plasma sugar 278mg., plasma chlorides 580mg. per 100cc. R. B. C. 6,530,000, red cell volume 46%, hemoglobin 91%.

100gm. of glucose by mouth produced a high and prolonged rise in plasma sugar. Glycosuria continued throughout the experiment. The increase in sugar content of the plasma produced hydremia, as shown by the decrease in plasma chlorides from 580 to 553mg. per 100cc., in red cell volume from 46% to 42%, and in red blood count from 6,530,000 to 5,950,000. Hemoglobin showed a gradual fall throughout the experiment. The urine output for the first hour following the administration of glucose was only 93cc. The output during maximum hyperglycemia was 205cc. To this extent there was a parallelism of hyperglycemia and diuresis; nevertheless the greatest polyuria of 800cc. (in 2 hours) occurred between the 5th and 7th hours, after the plasma sugar had fallen appreciably. Blood pressure decreased during hyperglycemia.

Case 173. — M. W. Table 15, Chart 15. May 8, 1920.

Female, Hebrew, 36, married, housewife.

Case of very severe and rapidly progressive diabetes, admitted March 1, 1920, with acidosis of the dyspneic type, which responded

readily to treatment. She was kept on a diet of 20gm. of protein with alternating fast days for five weeks, but glycosuria was uncontrollable and the blood sugar was usually about 300 to 400mg. per 100cc. The urine contained sugar at the time of this experiment.

Preliminary period: With constant fluid intake of 200cc. water per hour the urine volumes were irregular, ranging from 52 to 314cc. The plasma sugar before giving glucose was 366mg. and the plasma chloride 590mg. per 100cc. R. C. V. 37%, hemoglobin 83%, R. B. C. 4,780,000.

50gm. of glucose was given. The observation period lasted 12 hours. The plasma sugar showed the typical prolonged curve of severe diabetes. It reached a maximum of 0.592% in two hours and maintained a content of 0.500% for 6 hours. During this time the red cell count rose. There was a marked fall in the red cell volume from 37% to 28% at the end of the second hour, when the plasma sugar was at a maximum. Plasma chlorides showed no definite changes. Hemoglobin was also irregular, but in general fell.

The urinary output showed definite periods of oliguria and polyuria in relation to the height of the blood sugar, oliguria being most marked at the time of the highest glycemia. At the end of the second hour the urine volume dropped to 84cc., when the plasma sugar was at its height, namely 0.592%. There was likewise a small output the following hour, while there was a continuation of the high sugar at 0.556%. Polyuria began with the fourth hour, and increased at the fifth hour, when there was an output of 330cc. For the sixth, seventh and eighth hour periods the output was 240, 205, and 234cc. respectively, with a fall in the plasma sugar to 0.466%. In this case the water retention ceased when the blood sugar began to decline.

Case 219. — C. A. R. Table 16, Chart 16. April 25, 1920.

Female, 41, American, married, housewife.

Case of extremely severe diabetes of 8 years' duration. Lost a great deal of weight. Patient was careless with diet, often had glycosuria, and was seriously emaciated. At admission she had severe acidosis with dyspnea. Plasma sugar 0.500%, plasma nitroprusside test heavy, CO₂ capacity of plasma 40.0 vol. per cent. As carbohydrate promised therapeutic benefit in this case, a glucose tolerance test was performed.

Preliminary period: The urine volume before the administration of glucose was irregular. The output for the first hour was 28cc. and for the second 194cc. The chemical findings were as follows: Plasma sugar 387mg., plasma NaCl 620mg. per 100cc. R. B. C. 5,848,000, hemoglobin 107%, red cell volume 42.9%.

Only 25gm. of glucose was given. The plasma sugar showed a marked and prolonged rise. Hyperglycemia did not cause oliguria, but on the contrary the output exceeded the intake at each hourly interval throughout the experiment. The blood volume apparently was little altered, but such changes as were indicated by the corpuscle count and volume, hemoglobin, and plasma chloride were in the direction of dilution during the hyperglycemia.

Case 187.—F. G. Table 17, Chart 17. March 9, 1920.

Female, 14, American, school girl.

Case of severe diabetes complicated by pulmonary tuberculosis. Acute onset six months previously. Untreated, the patient grew progressively worse, very emaciated, with chronic acidosis. Physical examination, except for active tuberculosis, was negative. The test was performed while glycosuria was present.

Preliminary period: The urine volumes were 105cc. and 45cc. per hour on a constant water intake of 200cc. R. B. C. 5,500,000, hemoglobin 108%, R. C. V. 32%. Plasma sugar 402mg., plasma chlorides 555mg. per 100cc.

Only 50gm. of glucose was administered. The plasma sugar curve was characteristic of severe diabetes, rising within one hour from 402 to 616mg. per 100cc. During hyperglycemia the plasma chloride decreased and continued to decrease throughout the experiment. Hemoglobin dropped to 58%, R. B. C. to 3,690,000 during hyperglycemia. The hemoglobin maintained a dilution below 69% and the corpuscle volume remained at 37% for 4 hours. The urinary output continued inferior to the fluid intake during this 4-hour period of maximum hyperglycemia and hydremia. There was heavy glycosuria throughout, though the record of urine sugar analyses was unfortunately lost. The delayed diuresis was more marked in this case than any other of the series. A tremendous output of 810cc. occurred at the fifth hour, when the plasma sugar had fallen to its lowest figure. Diuresis continued further during the next two hours, when the volumes were respectively 380 and 316cc.

Case 283.—E. J. O. Table 18, Chart 18. May 16, 1920.

Male, 22, single, American, clerk.

Case of severe diabetes of supposedly five months' duration, with loss of 40 pounds in weight. Symptoms of acidosis for one month. Heavy acidosis and lipemia at the time of this experiment.

Preliminary period: The urine output was 120, 130 and 120cc. per hour for 3 hours preceding the administration of glucose. Plasma sugar 307, plasma chloride 460mg. per 100cc. R. B. C. 4,030,000, hemoglobin 105%, R. C. V. 33%.

50gm. of glucose was given. The plasma sugar rose slowly from 307 to 461mg. per 100cc. at the end of two hours. The fluid output was little affected by the glucose. Oliguria did not occur as in most of the mild cases. The output approximately equalled the intake of 200cc. There was no consistent change in the water content of the blood, as judged by the plasma chloride, cell volume and blood counts. 24gm. of glucose was excreted in seven hours; nevertheless the late diuresis observed in so many cases did not occur.

Case No. 85.—C. A. S. Table 19, Chart 19. March 26, 1920.

Male, 31, American, single, physician.

Case of very severe diabetes in a young man, with acute onset 5½ years previously. Kept free from glycosuria but with hyperglycemia for two years, the trouble gradually progressed and tolerance de-

creased. For eight months prior to admission the diet was about 500 calories with 5 grams of carbohydrate. After admission it was possible gradually to increase the diet to 1200 calories, and the patient remained on this for a period of six months before the experiment. The study in this case was thus made upon severe diabetes under perfect dietary control, and is in contrast to the studies in the other severe cases Nos. 173, 219, 187 and 283, which were in the active stages of diabetes when the experiments were carried out.

Preliminary period: The urine volumes were 95cc. and 100cc. per hour on the usual water intake of 200cc. per hour. Plasma sugar 123mg. and plasma chloride 615mg. per 100cc. R. B. C. 5,616,000, hemoglobin 76%, R. C. V. 33.8%.

Only 25gm. of glucose was given. The blood sugar curve was typical of a severe case, reaching a maximum in one hour and not returning to normal for 8 hours. As in the severe case No. 283, the anti-diuretic effect of glucose was not marked, the urine volumes being 90 and 83cc., and was less noticeable than in the severe cases Nos. 187 and 173. Diuresis did not occur when the plasma sugar returned to normal, as in the normal and mildly diabetic cases. During hyperglycemia the plasma chlorides decreased from 615mg. per 100cc. to 605 and 585mg. per 100cc. during the second and third hours. R. C. V. showed very little change. R. B. C. decreased distinctly during hyperglycemia, while the hemoglobin rose. Glycosuria remained absent.

CONTROL TESTS WITH SALT AND WATER

Case No. 215.—A. N. Table 20. May 17, 1920.

Male, 24, single, Hebrew.

Case of moderate diabetes well under control. Plasma sugar had been normal for 5 months previous to the test, on a diet of 1400 calories.

Preliminary period: 200cc. of water was given each hour prior to the administration of the salt, and the urine volume each hour averaged above 200cc. The red cell count was 5,400,000, hemoglobin 77%, red cell volume 42.7%, plasma chloride 565mg., plasma sugar 133mg. per 100cc.

10gm. of pure sodium chloride was administered in the usual 200cc. of water. The rise in plasma chloride was similar to the rise in plasma sugar in a severe diabetic case after the administration of glucose, the content rising from 565 to 605mg. and remaining elevated for several hours. The anti-diuretic effect of salt was similar to that of glucose. The urine volume was reduced for 2 hours, and then gradually increased until the 6th hour, when a mild diuresis occurred, after the plasma chloride had begun to decrease. The maximum chloride output in the urine occurred in the 2nd to the 4th hours. The plasma sugar showed no change other than that expected to occur during such a fast.

Administration of salt produced no change in red blood count. A slight decrease in the red cell volume occurred during the maximum

concentration of the plasma chloride, and hemoglobin showed a slight increase.

Same patient. — Table 21. June 7, 1920.

This experiment was performed as a control to note the effect of a constant fluid intake upon the various blood elements and upon urinary excretion, as also to check the methods employed. The results were practically negative. There was no change in red cell volume, red blood counts or hemoglobin at any time. The urine volume was practically constant, as were the specific gravity and percentage of urine chloride.

The plasma chlorides showed a gradual decrease, probably due to the loss of chloride in the urine.

SUMMARY

EFFECT OF GLUCOSE INGESTION UPON WATER EXCRETION

Glucose taken orally generally proved to be an anti-diuretic. By its osmotic power it first caused water retention, followed by a release of the fluid causing a period of diuresis. The oliguria produced was most marked at the height of the hyperglycemia and did not cease until the excess of sugar was utilized or disposed of. Since oliguria and diuresis occurred at different intervals, and varied with the amount of sugar contained in the blood and the form of curve it produced, it will be best to describe these changes in the various types of cases observed.

In Non-diabetics. — Chart 20 represents a composite of the blood sugar curves and the average hourly urine output in 5 non-diabetic cases. The output during a preliminary period before giving glucose averaged 105cc. per hour for 3 hours. It will be noted that the excretion increased hourly during this period until the 3rd hour, when the output just equalled the intake of 200cc. This deficiency of water excretion during the preliminary period was due to the fact that the experiments were begun early in the morning before food or fluid was taken, and part of the intake of 200cc. was used to replace the body fluids lost during the night. Following glucose administration the blood sugar rose rapidly and fell quickly to normal. During maximum hyperglycemia there was water retention, and the urinary output fell sharply and remained low until the disappearance of the excess sugar from the blood. In 2 cases the volume fell to less than 50cc. per hour. Follow-

ing this period of water retention the volume gradually increased until the 4th hour. Then came a period of sharp diuresis. In one case it occurred at the 3rd hour. The average hourly output for the diuretic period was 300cc. In one case it amounted to 340cc. Following diuresis, a secondary oliguria occurred at the 6th hour, this followed in turn by a secondary diuresis at the 7th and 8th hours.

In Mild Diabetes.—In these cases the plasma sugar, with an average of 0.126% while fasting, was slightly higher at the beginning of the test than in the normal subjects. Water excretion during the preliminary period was small in amount and gradually increased to 100cc. at the end of the period. The composite plasma sugar curve of the 9 cases shows that an average maximum of 0.260% was reached at the end of an hour following glucose administration and that it declined slowly and steadily to normal at the end of 4 hours. There was a small secondary rise about the 6th hour, in typical tests in this type of case.

Oliguria followed glucose administration, as shown in the composite curve in Chart 21. The average hourly output fell from 100cc. before giving glucose to 65cc. for the first hour period after its administration. Specific gravity was increased in consequence of the diminished volume, and sugar appeared in the urine in greater concentration at this period than in any subsequently. In 4 cases the output was less than 50cc. It was decreased to such an extent in case No. 224 that no specimen could be obtained at the end of the first hour.

During the course of the high blood sugar in these cases the body continued to retain water, and excretion was kept low for a longer period of time than in the normal controls. In case No. 230, which was one of mild diabetes with heavy glycosuria at the time of the test, 100gm. of glucose produced a slow rise in plasma sugar to 0.724% at the end of 2 hours. Three more hours were required for it to return to its original figure, and oliguria continued during this time. The affinity of the tissues and blood for fluids during hyperglycemia ran more or less parallel with the quantity of sugar present and the duration of the sugar curve, therefore the release of the retained fluid by the blood and tissues often occurred later in the mildly diabetic than in the normal individuals. In case

No. 230 it occurred during the 6th and 7th hours. The diuresis following the fall in blood sugar was also longer and lasted over two hourly periods.

In Severe Diabetes.—During a preliminary period of 3 hours, before glucose administration, the average urinary output was 100cc. per hour. Sugar was present in the urine in large quantities in 4 of the severe cases during the preliminary period, but it will be seen that the urinary volume was small and practically the same as in the normal and mildly diabetic subjects. The plasma sugar for the preliminary period averaged 0.365%. Following glucose administration the plasma sugar rose steadily and reached an average maximum of 0.545% at the end of 1 hour. Oliguria generally was perceptible in the first hour, the volume dropping to an average of 80cc. In a minority of cases glucose acted as a diuretic, as noted in the individual records. Throughout this group, though the plasma sugar rose higher after glucose administration than in the mildly diabetic cases, the accompanying water retention was decidedly less. Even in the cases with primary oliguria, the urinary volume gradually increased while the plasma sugar still remained very high. In exceptional cases this secondary diuresis was great. In case No. 187 it amounted to over 800cc. at the 5th hour.

RELATION OF CORPUSCLE VOLUME TO HYPERGLYCEMIA

Red cell volume was diminished during the course of hyperglycemia in 16 of the 19 cases. In 11 of these the decrease accompanied the maximum hyperglycemia, and in 5 it came during the decline. In normal subjects the fall in volume occurred early. In 2 cases it came in the 30 minute period, and not later than 2 hours in any of them. The cell volume promptly returned to its original figure after the disappearance of the hyperglycemia. This decrease in cell volume was slightly greater in the normal than in the mildly diabetic subjects. The average decrease in the former was 14% as compared with 10% in the later. The diminution of cell volume persisted through the longer period of hyperglycemia, so that the return to the original value was not as early as in the normal subjects. This is well shown in the graphic charts of cases No. 241, 263 and 259. The mild cases No. 204 and 201 resembled the normals in that the plasma sugar rose

only moderately and soon returned to normal, and was accompanied by a prompt decrease in cell volume at the height of hyperglycemia, with return to normal as soon as the hyperglycemia disappeared.

In 4 of the 5 cases of severe diabetes hyperglycemia was accompanied by decrease in cell volume. The fall occurred at the height of hyperglycemia in 3 cases, and shortly after the maximum in 1 case. In the 5th case the red cell volume was not diminished. A secondary rise in volume occurred at the 6th hour in 3 cases, followed by a decrease in volume below that found at the beginning of the experiment. The fluid intake exceeded the output in two of these, so there may have been actual blood dilution.

RELATION OF HEMOGLOBIN AND RED CELL COUNTS TO HYPERGLYCEMIA

Hemoglobin determinations were made in 17 cases. Eleven of these showed decrease in hemoglobin at the time of the rise in blood sugar. In the majority of cases the fall in hemoglobin was accompanied by decrease in the cell volume, as shown in the charts of the respective cases. The most marked change occurred in the severe cases. Four of these showed a fall in hemoglobin when the plasma sugar was high. In the severe case No. 173 the hemoglobin fell from 83% to 74% after the administration of glucose. In 2 other severe cases, Nos. 219 and 187, a rapid fall of hemoglobin occurred within 30 minutes after glucose administration.

In 6 cases of mild diabetes the rise in sugar was accompanied by a fall in hemoglobin. Three of these showed the decrease during maximum hyperglycemia, while in 3 others the fall occurred during the decline.

Demonstration of hydremic plethora by means of red corpuscle counts is of course difficult, but in this series the results obtained in 5 cases were sufficiently marked to indicate an undoubted hydremia in consequence of glucose ingestion. The greatest changes of this sort were found in the severe cases, as 3 out of the 5 showed decrease in red counts during hyperglycemia. It was most marked in Case No. 187, in which 50gm. of glucose produced a rise in blood sugar from 0.400% to 0.616%, with a fall in red count from 5,550,000 to 3,690,000.

With the fall in count there was also a great fall in hemo-

globin. The red cell volume however remained unchanged. In order to maintain this cell volume with a decreased number of cells, the size of the individual cells must evidently be increased during this time. The frequent contradictions between cell volume and cell counts can thus be understood, but the numerous discrepancies observed by both ourselves and other writers between hemoglobin and cell counts are not so easily explained.

RELATION OF FLUID ELIMINATION TO GLUCOSE EXCRETION

In the cases of mild diabetes water excretion was at its lowest during the first hour following glucose administration. More glucose, however, was excreted in the first hour than in any of the periods following. Chart 23 shows the average urinary volume and the total glucose excretion for each hour in all the cases of mild diabetes. The average hourly volume was at a minimum of 80cc. for the first hour after giving the glucose, while the average total sugar output amounted to 1.1gm. In the second hour period the volume increased to 175cc., while the total sugar output decreased slightly to 1.0gm. From this time on the volume increased, and at the 4th hour the output amounted to 220cc., while glucose excretion had fallen to less than 0.2gm. The fluid retention indicated by the oliguria was confirmed by the evidence of hydremic plethora during the period of hyperglycemia and glycosuria.

In the severe cases the opposite relation between fluid and glucose elimination existed. Water was generally retained during the first few hours, somewhat as in the normal and mildly diabetic subjects, and later came a period of diuresis. This diuresis occurred typically at the 5th and 6th hours, when also the greatest amount of glucose was excreted, the average hourly output being 5 and 6 grams. Chart 24 shows the relation between the excretion of sugar and water.

SALT AND WATER CONTROLS

A single control test with ingestion of 10gm. of sodium chloride gave results essentially similar to those with glucose, namely a marked rise in the plasma chloride concentration with coincident oliguria, followed by increase of the urine volume after decline of the plasma chloride values. Changes

in the blood volume were doubtful during the period of oliguria, but there was apparent hydremia in the later part of the experiment, and this may have been the cause of the polyuria at this time.

A similar control with water alone was negative.

CONCLUSIONS

1. Glucose ingestion produces hyperglycemia attended with oliguria in normal and in many diabetic subjects. The accompanying fall in hemoglobin, red cell volume and to a less degree in red cell counts indicates a probable hydremic plethora at the same time, or at least serves to rule out any concentration of the blood rather definitely. The usual fall in the plasma chloride concentration is further evidence in favor of a retention of water in the blood or tissues or both.

2. The point which it is desired to emphasize is the apparent dilution of the blood during the period of hyperglycemia and oliguria in all typical cases. It thus seems possible definitely to exclude the assumption that the oliguria is due to concentration of the blood through the osmotic withdrawal of water from it by the glucose in the intestine.

3. Another easy assumption has been that glucose acts as a diuretic by its osmotic influence in the kidney. It might thus conceivably increase the quantity of glomerular filtrate, or cause water excretion through the tubules, or prevent resorption of water in the tubules, according to the theory of renal function adopted. The experimental facts contradict this assumption, inasmuch as oliguria is typically just as pronounced or even more so when there is marked glycosuria in addition to hyperglycemia and hydremia. Thus, in one of our cases oliguria existed with 2.86% glycosuria.

4. In a minority of the diabetic cases, especially of the severe group, glucose lacked the above anti-diuretic influence and even served as an active diuretic in accord with former views on the subject, producing polyuria with or without hydremia. It should be noticed that in no case was the diabetes "total". Only a part of the glucose administered was either excreted during the experimental period or retained in the blood, so that proof is thus afforded of a partial re-

tention of power either to utilize sugar or at least warehouse it in the tissues. Under these conditions of partial diabetes, it is not surprising that the behavior toward diuresis was mixed, inclining sometimes toward the normal result and sometimes toward an abnormality which seems characteristic of diabetes.

5. No theoretical explanation of these differences will be attempted here. The functional state of the kidney must be one factor in diuresis, and it is known from the observations in paper No. 2 of this series⁹ and those of numerous other authors that long standing diabetes is attended by at least one alteration of renal function, namely a rise of the threshold for sugar. The variations in blood count, hemoglobin, etc., observed by ourselves and other authors may point to some similar change in the equilibrium of sugar and water between the blood on the one hand and the kidneys and tissues on the other, especially in severe diabetes. Any explanation, however, should take note of three experimental facts observed here. First, this diuretic peculiarity is not sharply diagnostic of diabetes. The mildest cases, for example, which retain a high degree of assimilative power, react with anti-diuresis like the normal, and their exaggeration of the height or duration of the normal glycemic curve after glucose ingestion may be accompanied by a similar exaggeration of anti-diuresis. Second, the differences are not dependent upon the quantity or concentration of sugar excreted. For example, the oliguria in some mildly diabetic cases with glycosuria is as pronounced as in normal cases with no glycosuria, and the differences in diuresis between different diabetics by no means correspond to the differences in glycosuria. Third, the severity of the diabetes appears to be a factor independent of hyperglycemia or glycosuria. For example, case No. 85 was actually very severe, with very low assimilative power but with normal blood sugar in consequence of long rigid treatment. A dose of glucose was given which raised the blood sugar to a level comparable to that of the mildly diabetic cases and produced no glycosuria, but the primary water retention and secondary diuresis characteristic of the mild cases was lacking.

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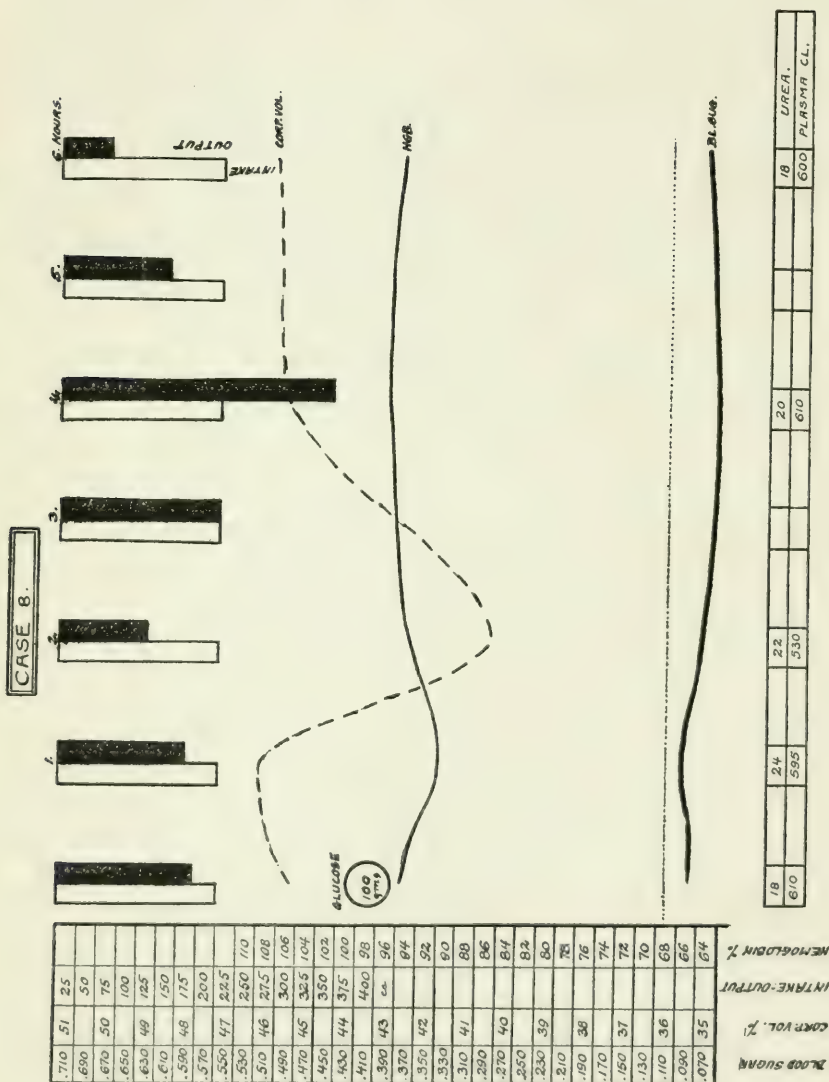
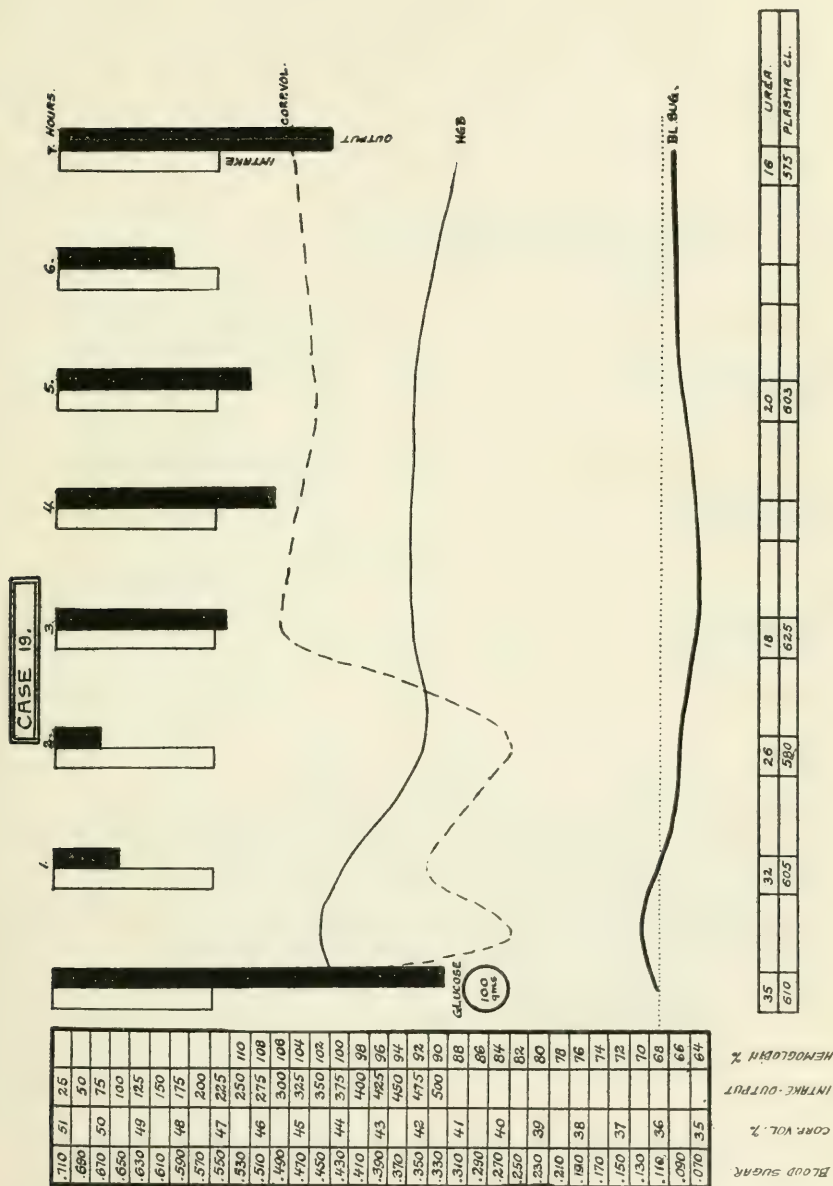
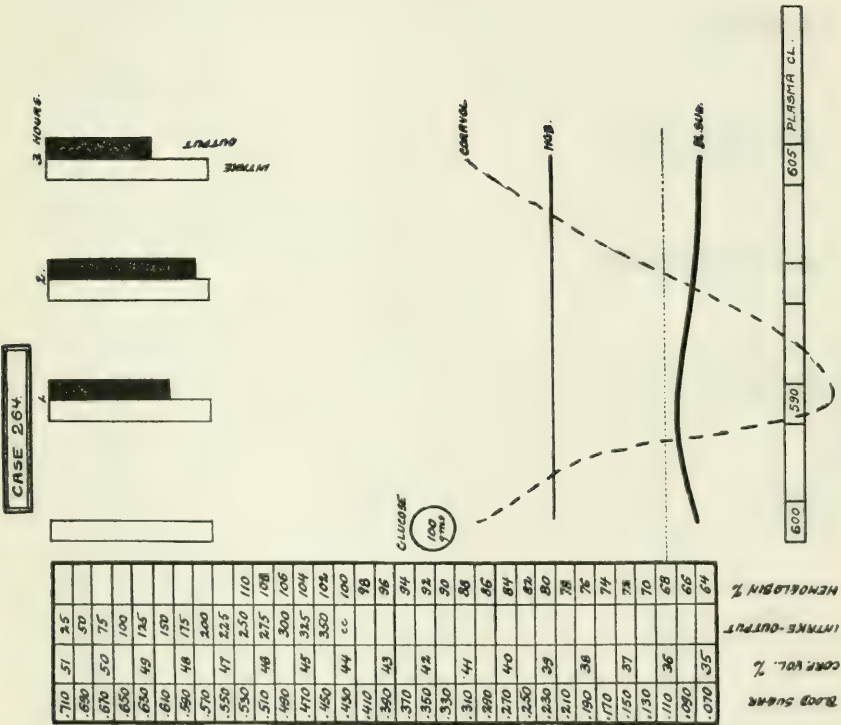


Chart 1.





CASE 188.

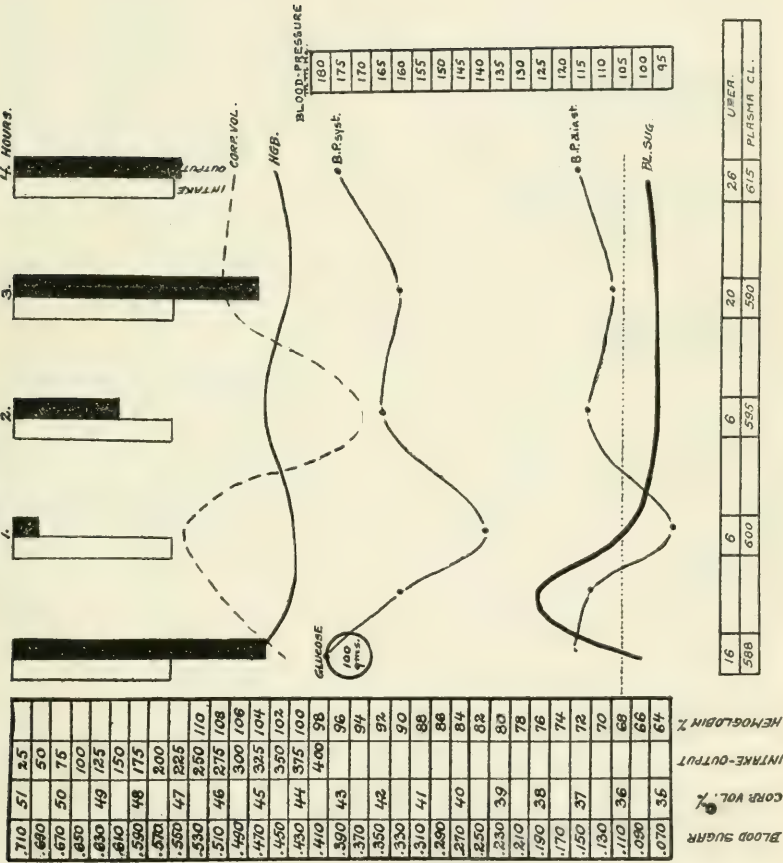
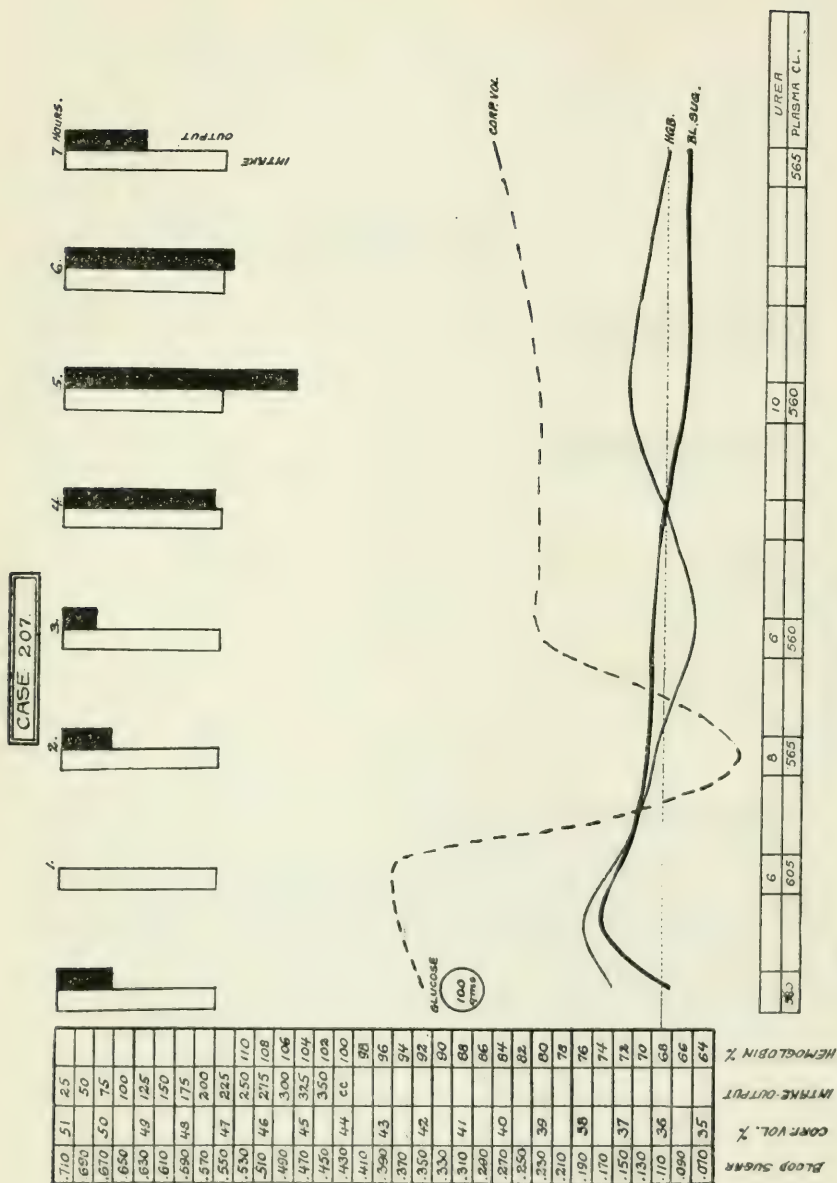
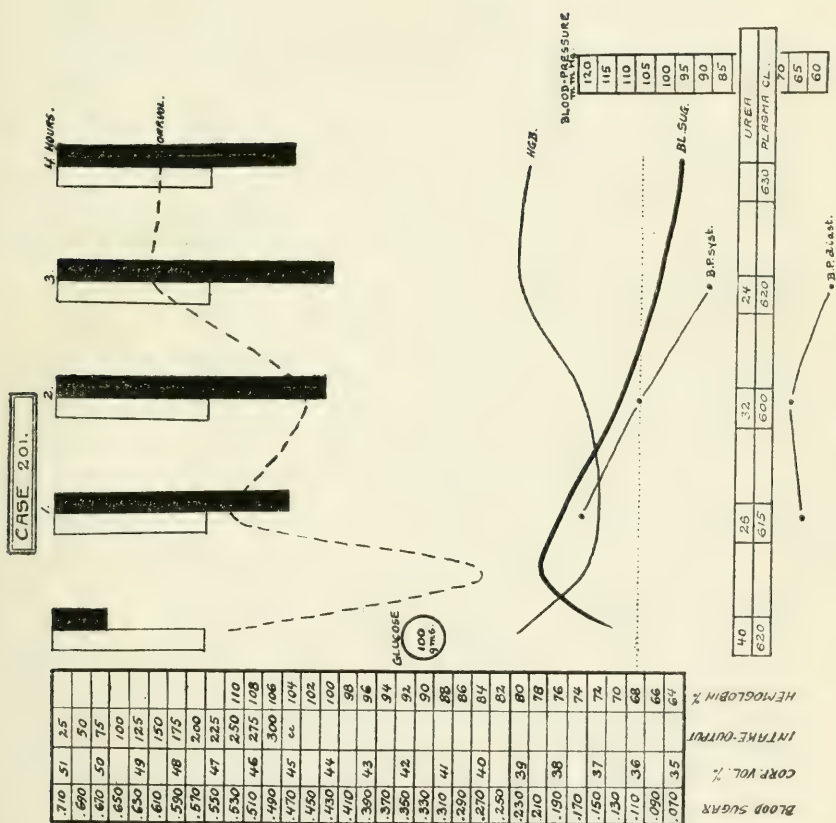
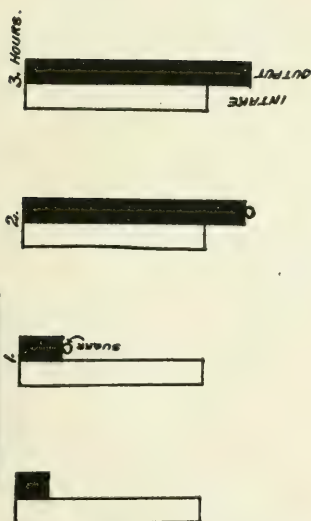


Chart 4.

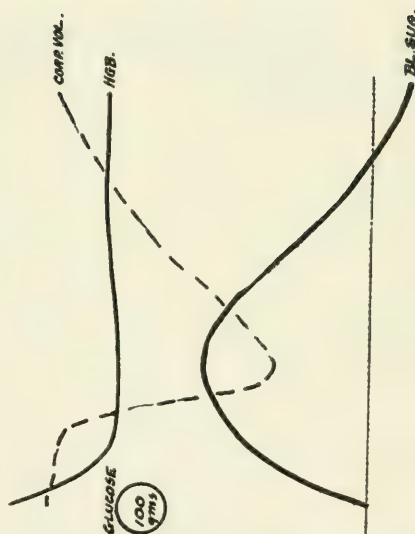




CASE 204.



BLOOD SUGAR	CORP VOL. %	INTAKE-OUTPUT	HEMOGLOBIN %
.710	51	25	
.690	50		
.670	50	75	
.650		100	
.630	49	125	
.610		150	
.590	48	175	
.670		200	
.560	47	225	
.530		250	110
.570	46	275	108
.480		300	106
.470	45		104
.450			102
.430	44		100
.410			98
.390	43		96
.370			94
.350	42		92
.330			90
.310	41		88
.290			86
.270	40		84
.250			82
.230	39		80
.210			78
.190	38		76
.170			74
.150	37		72
.130			70
.110	36		68
.090			66
.070	35		64



40	608	619	630	UREA.
633				PLASMA CL.

Chart 8.

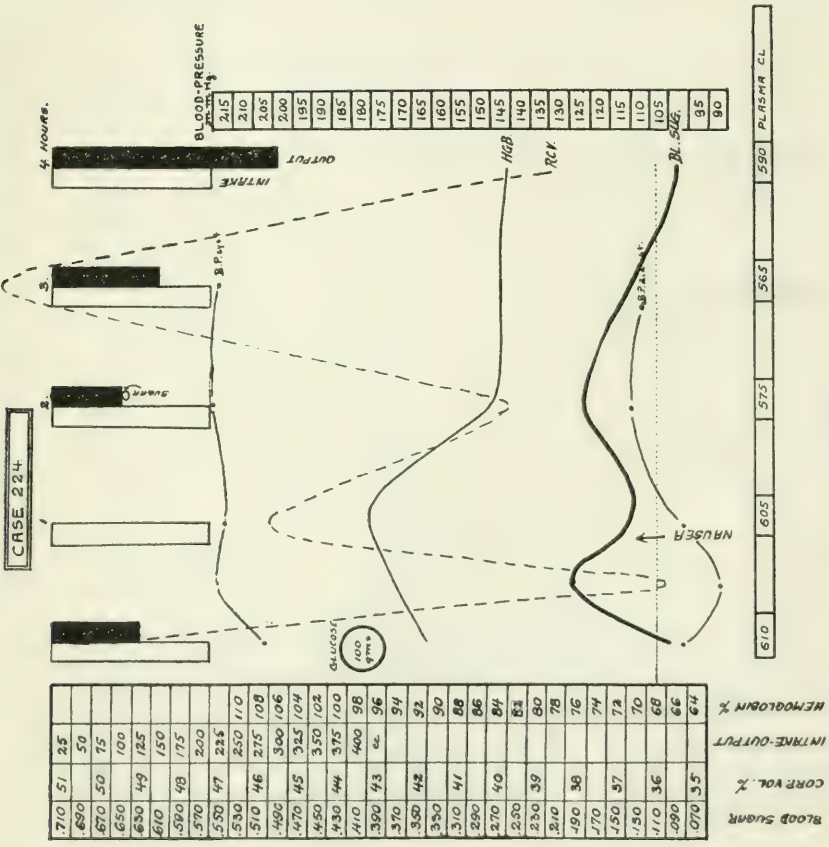


Chart 9.

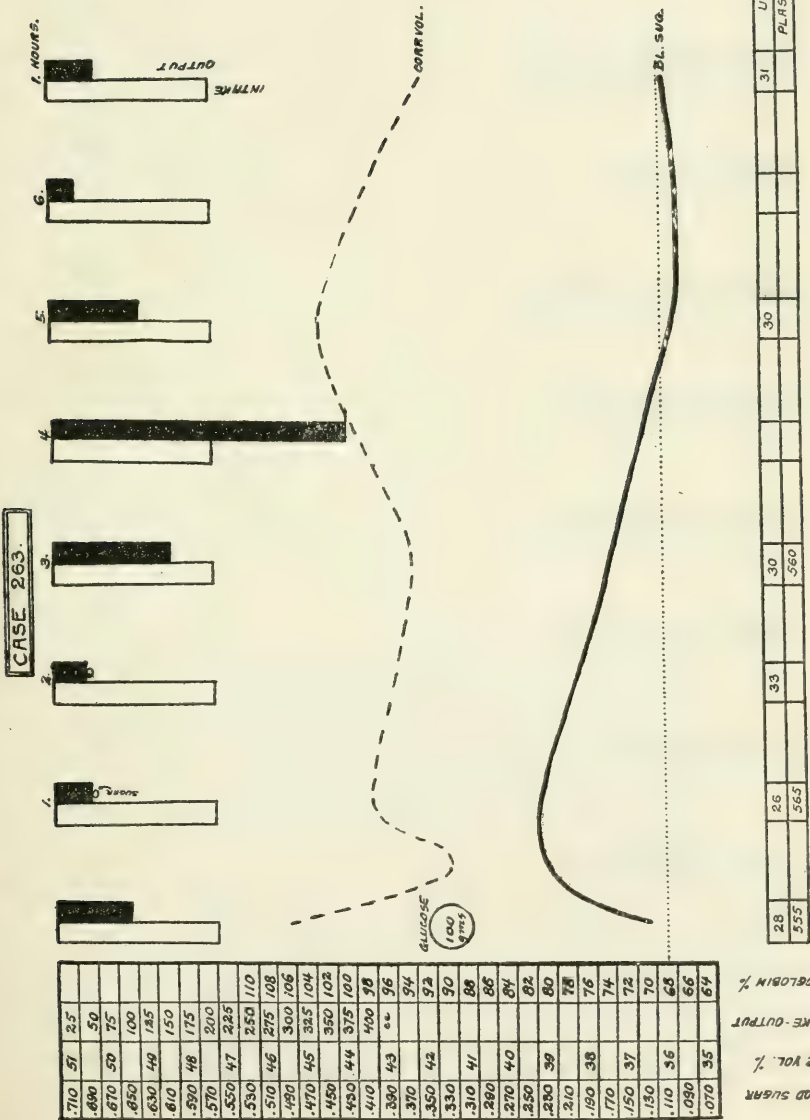


Chart 10.

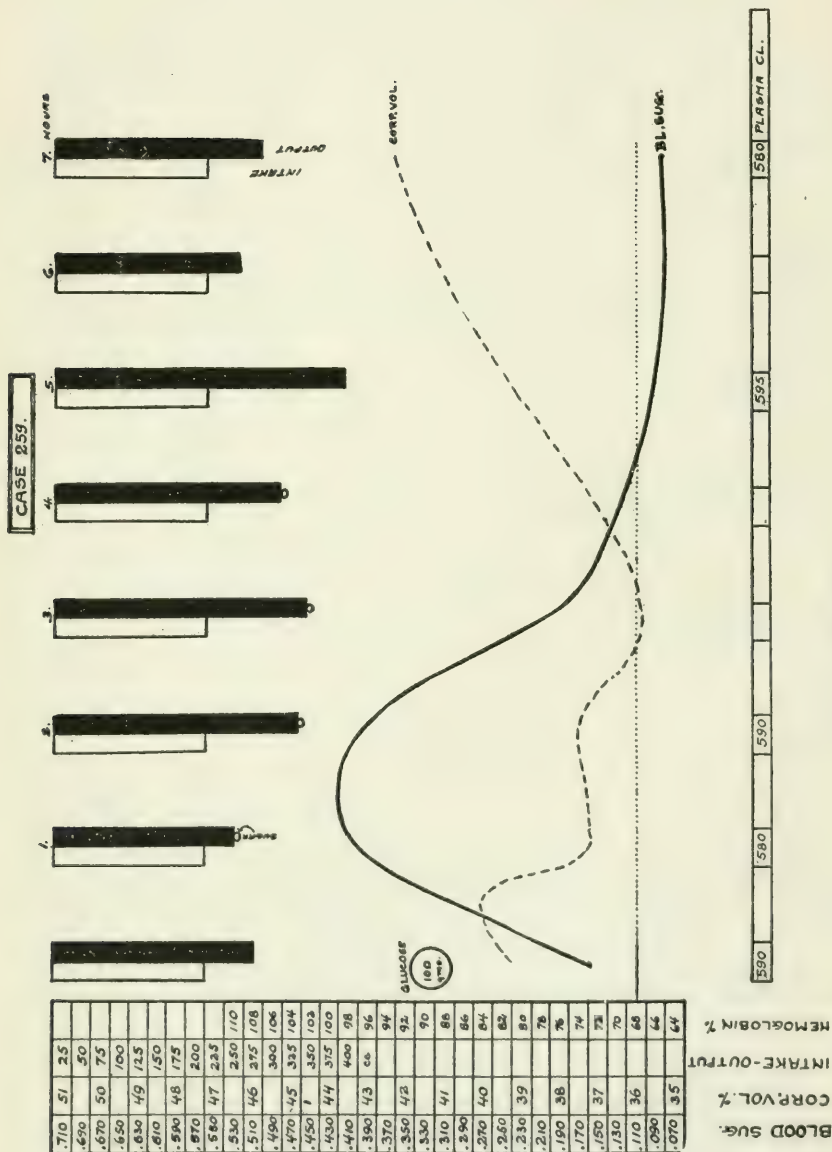
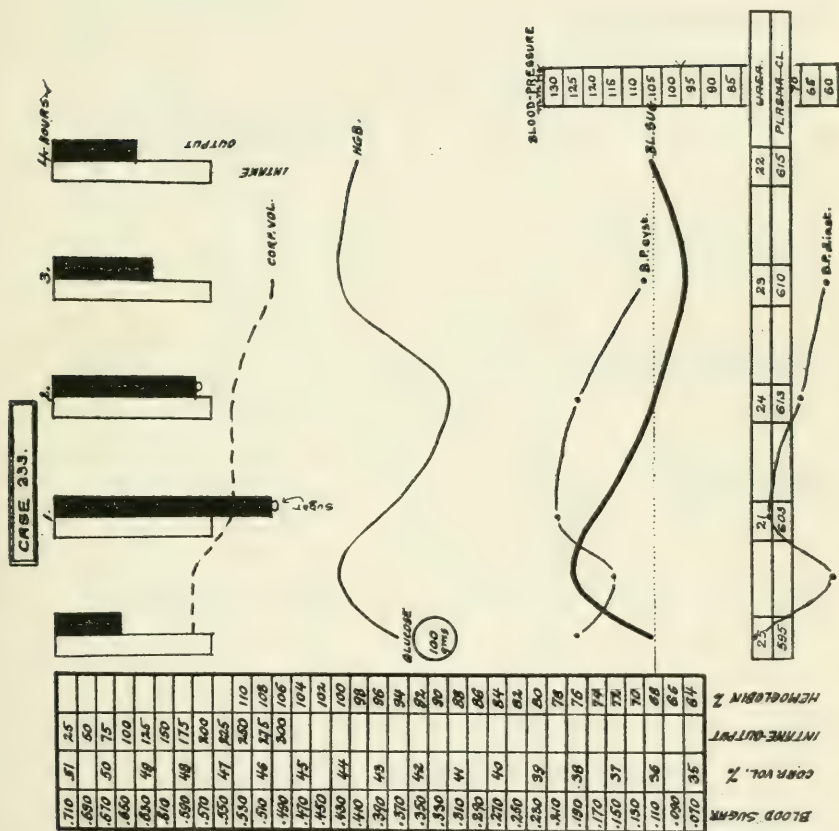


Chart 11.



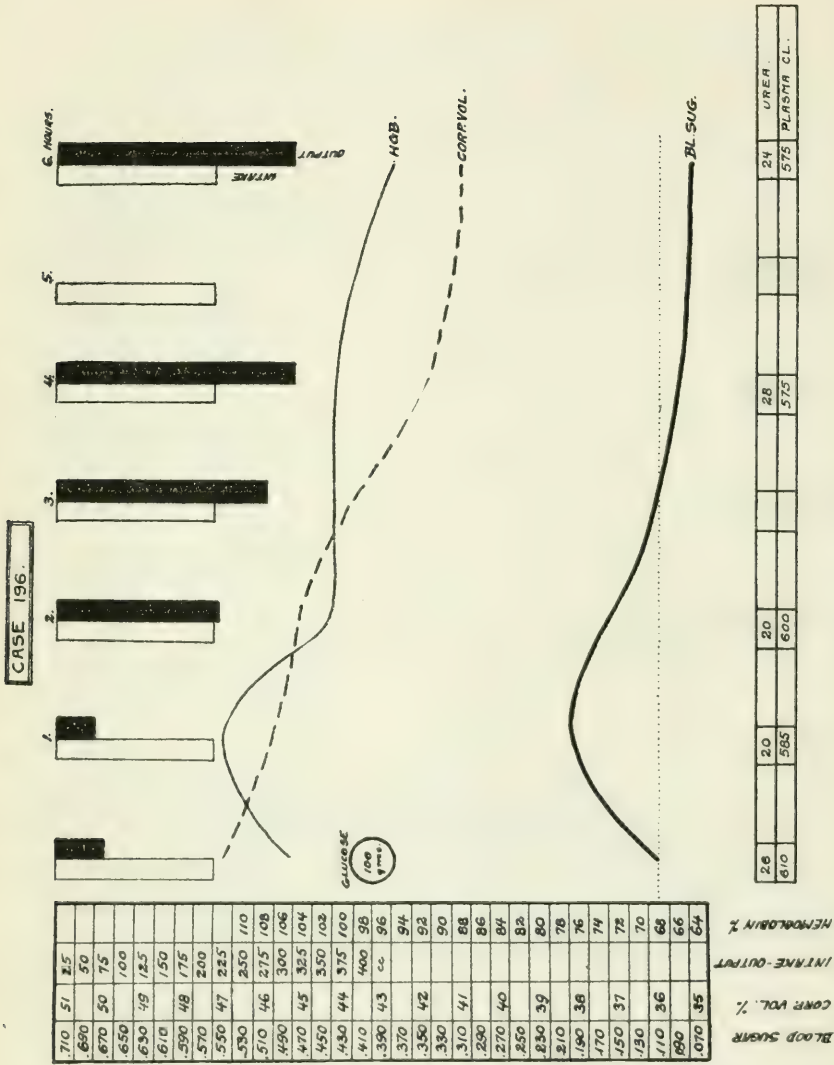


Chart 13.

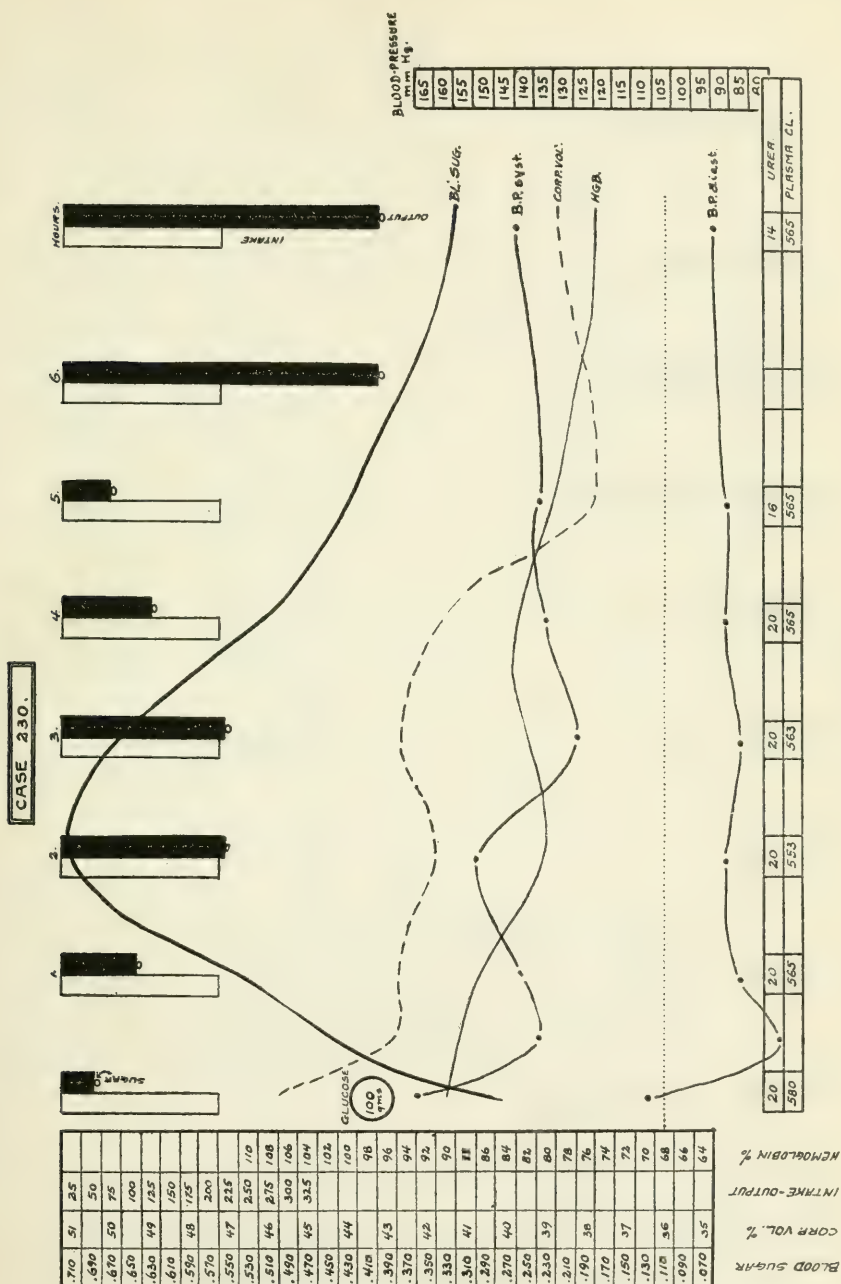
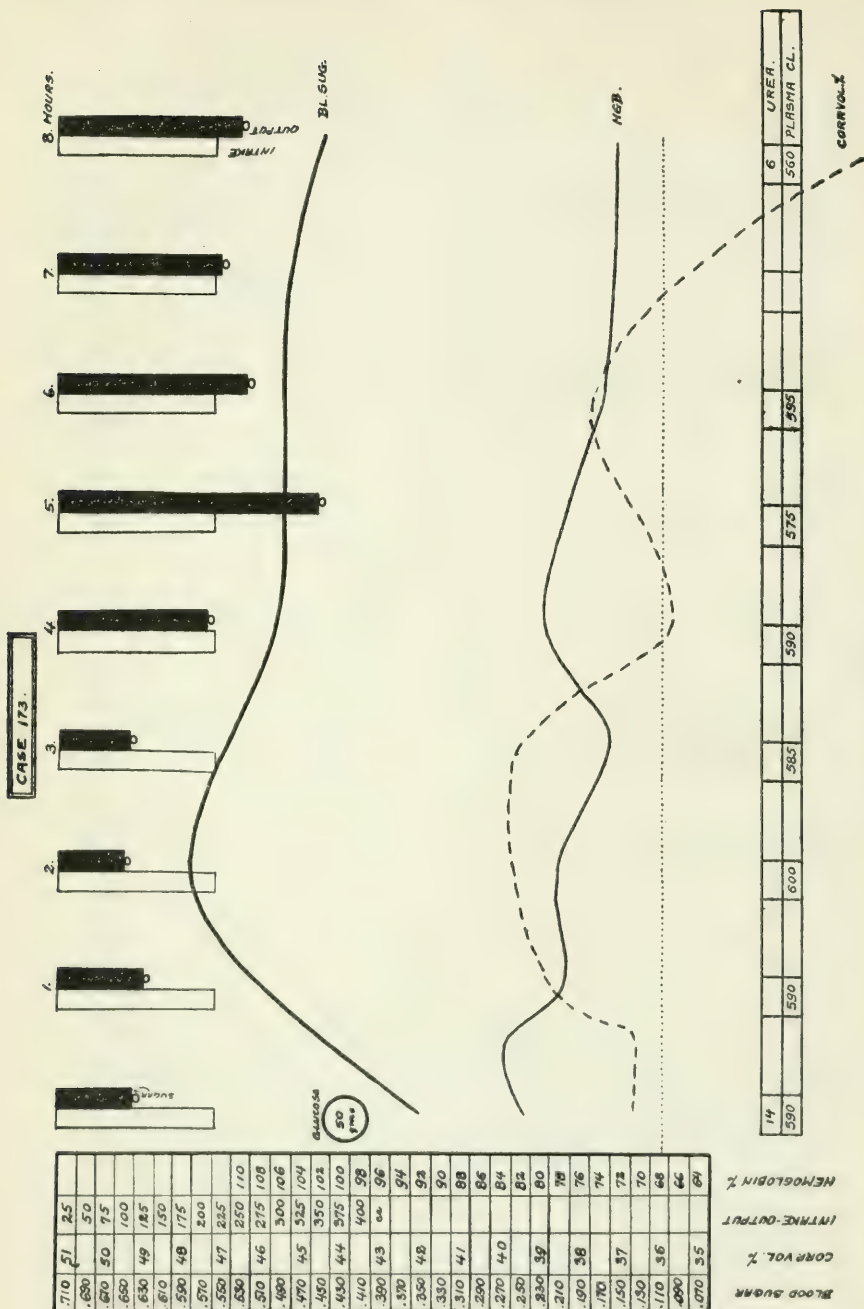


Chart 14.



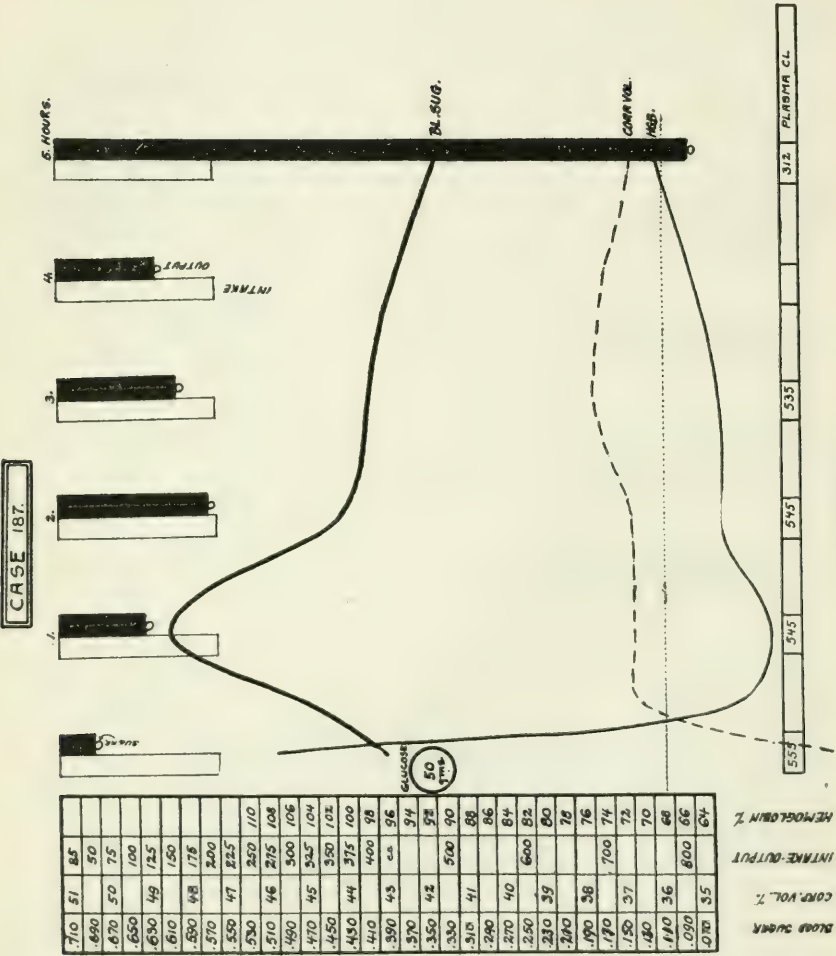
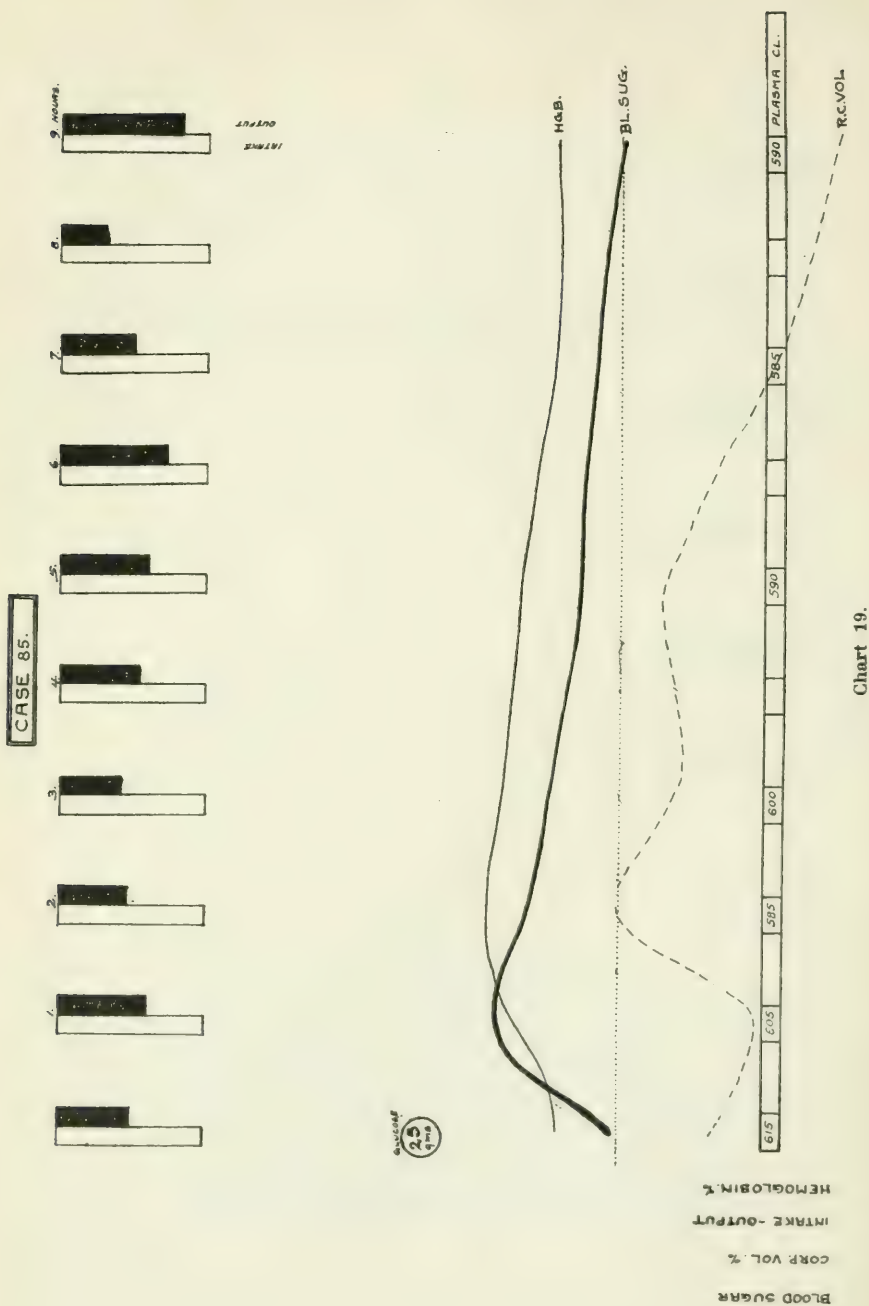


Chart 17.



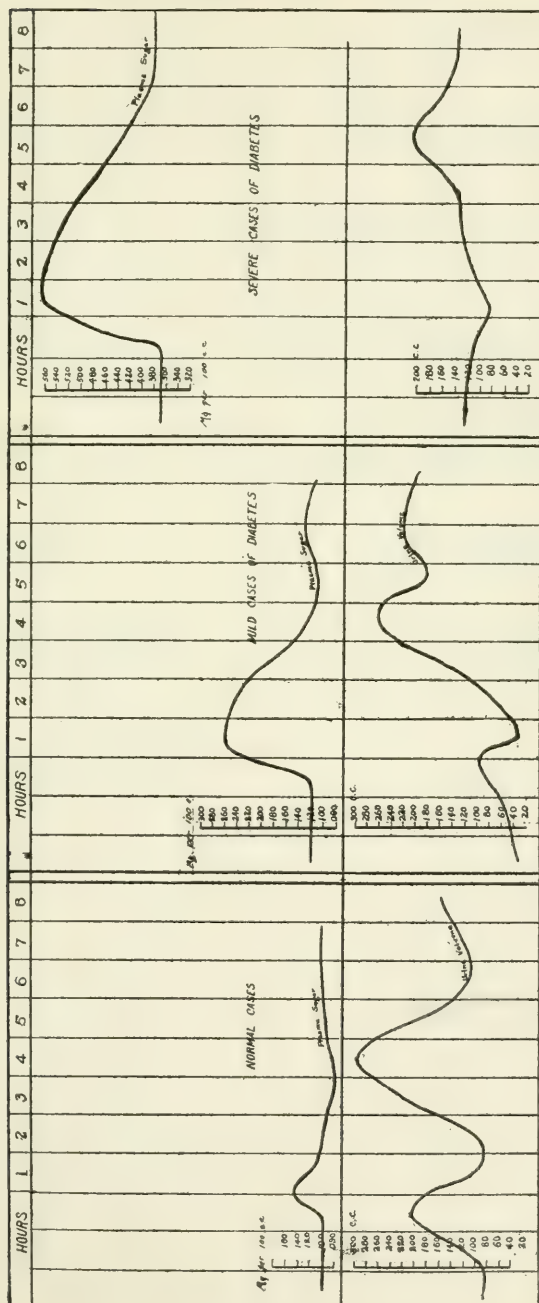


Chart 20.

Chart 21.

Chart 22.

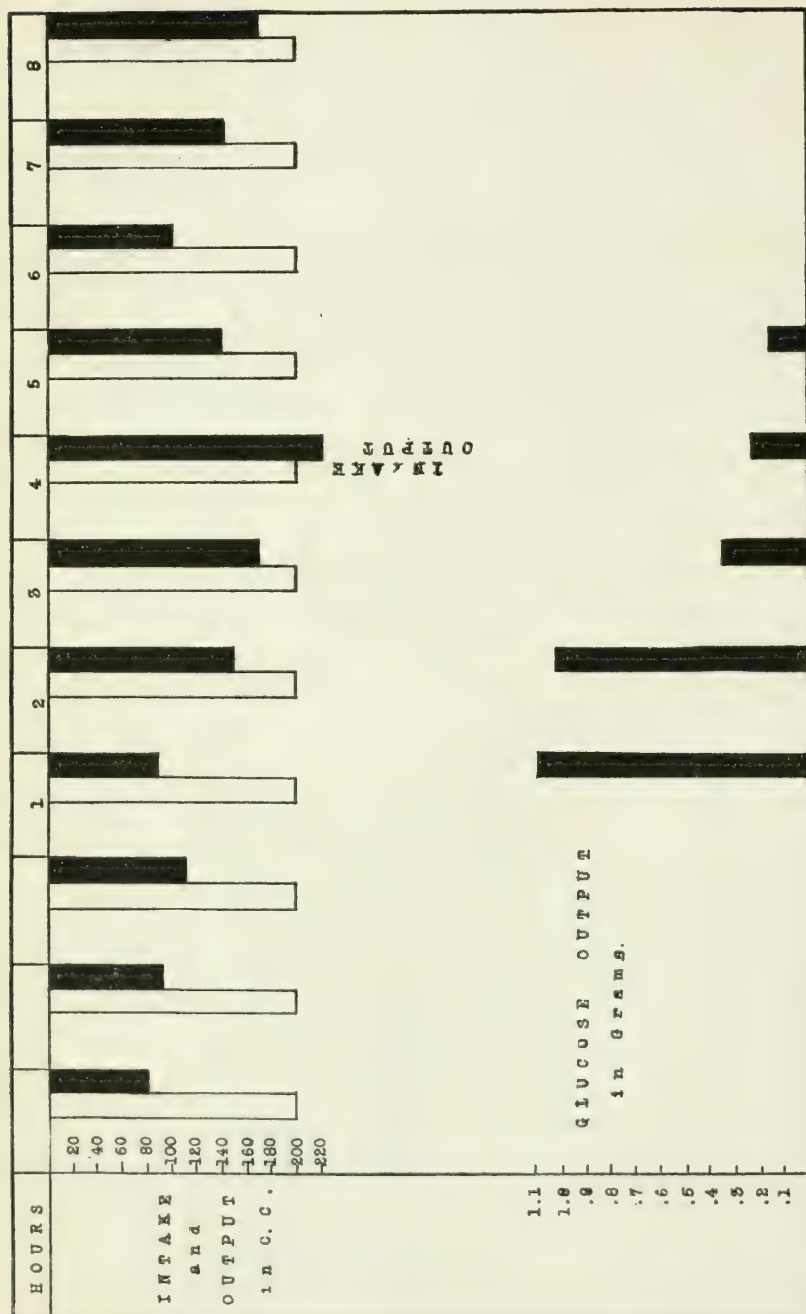


Chart 23.

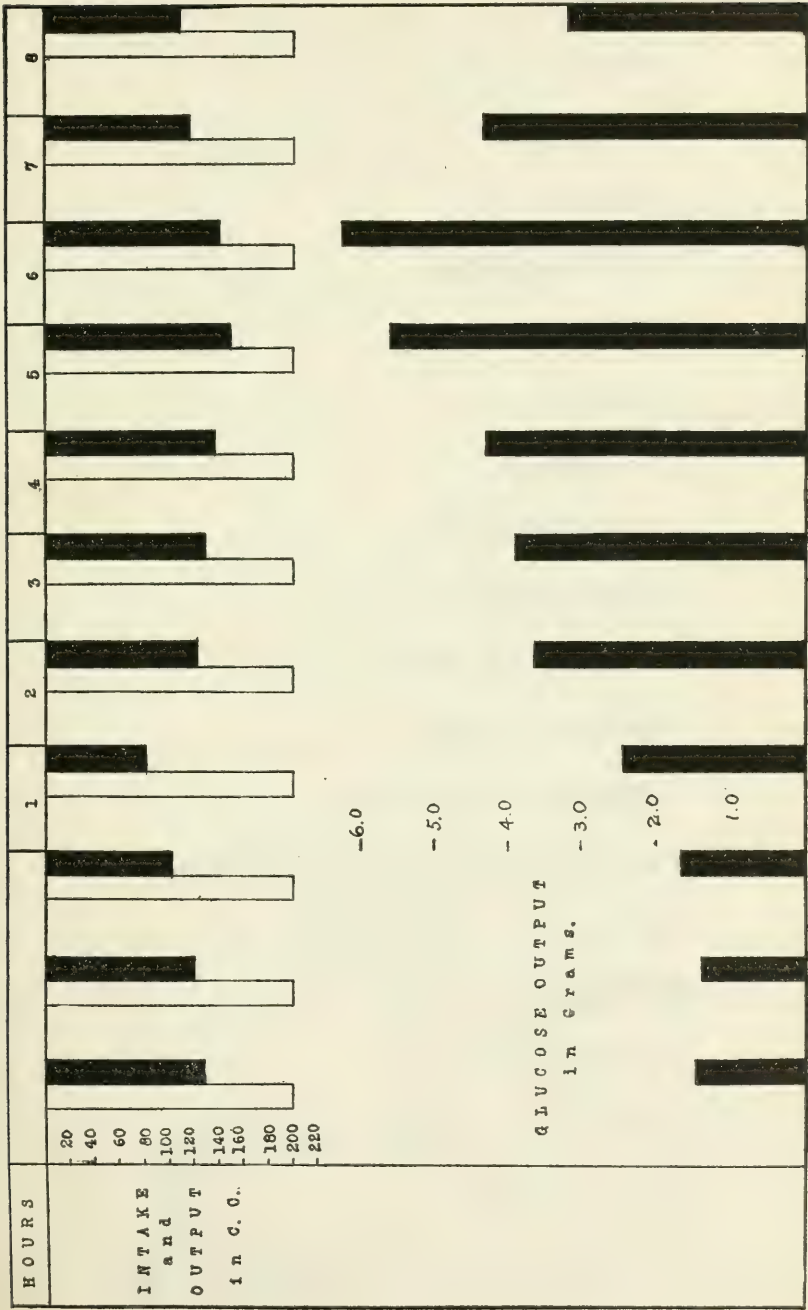


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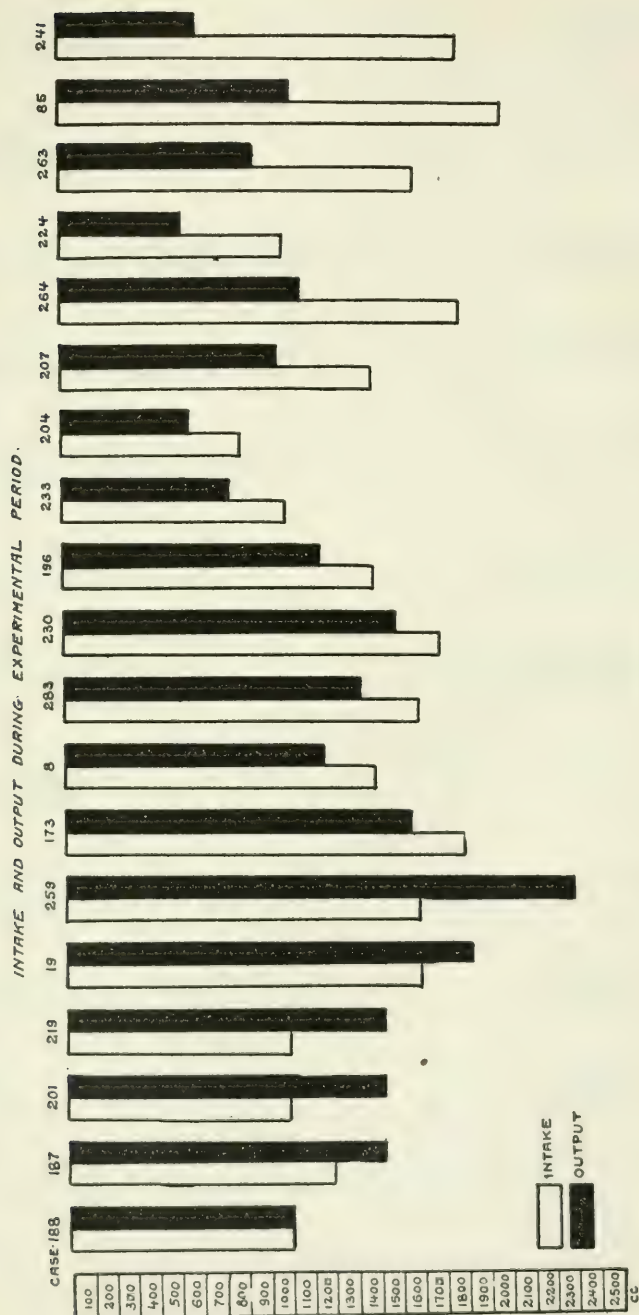


Chart 25.

TABLE 1.—Case No. 8. — June 7, 1920

Time	H g b. %	R. B. C.	Red Cell Vol. %	Plasma		Urine			Fluid Intake cc.
				Sugar mg. per 100 cc.	NaCl. mg. per 100 cc.	Vol. cc.	Sp. Gr.	NaCl. %	
8:00 *	—	4,500,000	—	—	—	165	1.007	0.60	200
9:00	96	—	45.7	101	610	170	1.006	0.10	200
9:30	94	4,700,000	46.3	117	610	—	—	—	—
10:00	92	4,700,000	46.5	117	595	160	1.007	0.12	200
11:00	95	4,680,000	40.7	101	530	110	1.007	0.18	200
12:00	—	—	—	—	—	200	1.004	0.12	200
1:00	97	4,200,000	45.8	71	610	340	1.004	0.08	200
2:00	—	—	—	—	—	135	1.008	0.16	200
3:00	96	4,500,000	46.1	88	600	60	1.014	0.24	200

* Drank 100 gm. glucose in 200 cc. water.

TABLE 2.—Case No. 19. — June 17, 1920

Time	R. B. C.	Red Cell Vol. %	H g b. %	Plasma		Blood Urea mg. per 100 cc.	Urine			Fluid Intake cc.
				Sugar mg. per 100 cc.	NaCl. mg. per 100 cc.		Vol. cc.	Sp. Gr.	NaCl. %	
6:00	—	—	—	—	—	—	215	1.027	—	200
7:00	—	—	—	—	—	—	70	1.020	0.60	200
8:00 *	6,344,000	47.3	101	124	610	35	490	1.006	0.12	200
8:30	6,440,000	40.0	103	140	588	30	—	—	—	—
9:00	6,280,000	42.2	101	121	605	32	85	1.016	0.74	200
10:00	6,200,000	40.0	93	100	580	26	60	1.019	0.96	200
11:00	6,000,000	45.8	94	82	625	18	215	1.007	0.36	200
12:00	—	—	—	—	—	—	275	1.007	0.44	200
1:00	6,688,000	45.0	94	102	603	20	245	1.005	0.32	200
2:00	—	—	—	—	—	—	145	1.007	0.36	200
3:00	6,160,000	45.6	89	111	575	16	340	1.004	0.18	200

* Given 100 gm. of glucose.

TABLE 3.—Case No. 264. — June 1, 1920

Time	R. B. C.	H g b. %	Red Cell Vol. %	Plasma		Urine			Water Intake cc.
				NaCl. mg. per 100 cc.	Sugar mg. per 100 cc.	Vol. cc.	Sp. Gr.	Sugar %	
6:00	—	—	—	—	—	—	—	—	200
7:00	—	—	—	—	—	18	—	0	200
8:00	—	—	—	—	—	18	—	0	200
9:00*	4,450,000	80	40.9	600	87	0	—	—	200
9:30	4,208,000	80	38.4	590	102	—	—	—	—
10:00	—	80	32.0	590	103	150	1.010	0	200
11:00	—	80	—	—	—	183	1.004	0	200
12:00	4,000,000	80	41.1	605	79	130	1.005	0	200
1:00	—	—	—	—	—	0	—	—	200
2:00	—	—	—	—	—	260	1.002	0	200
3:00	—	—	—	—	—	0	—	—	200
4:00	—	—	—	—	—	110	1.007	0	200
5:00	—	—	—	—	—	260	1.003	0	200

* Drink 100 gm. glucose in 200 cc. water.

TABLE 4.—Case No. 188. — April 10, 1920

Time	Blood Pressure	R. B. C.	H g b. %	Red Cell Vol. %	Plasma		Blood Urea mg. per 100 cc.	Urine				Fluid Intake c.c.
					NaCl. mg. per 100 cc.	Sugar mg. per 100 cc.		Vol. cc.	Sp. Gr.	NaCl. %	Sugar %	
8:00 *	182/120	6,300,000	106	44.6	588	98	16	320	1.013	0.94	0	200
8:30	164/116	6,900,000	102	46.2	610	204	12	—	—	—	—	200
9:00	142/ 95	6,090,000	102	47.2	600	116	6	32	1.014	0.94	0	200
10:00	168/116	5,490,000	105	42.8	595	88	6	130	1.008	0.03	—	200
11:00	164/110	5,380,000	102	46.3	590	88	20	310	1.003	0.03	—	200
12:00	178/118	6,000,000	104	46.0	615	96	26	210	1.001	0.02	0	200

* Given 100 gm. of glucose.

TABLE 5.—*Case No. 207.*—May 10, 1920

Time	R. B. C.	H g. b. c _g	Red Cell Vol. %	Plasma		Urine			Fluid Intake cc.
				Sugar mg. per 100 cc.	NaCl mg. per 100 cc.	Vol. cc.	Sp. Gr.	NaCl. %	
7:00-8:00	—	—	—	—	—	49	1.012	0.60	200
9:00	—	—	—	—	—	37	1.015	0.42	200
10:00*	4,800,000	74	42.3	108	580	71	1.012	0.72	200
10:30	4,300,000	77	42.8	181	580	—	—	—	—
11:00	3,700,000	73	43.1	164	605	0	—	—	200
12:00	4,100,000	70	34.4	135	565	66	1.013	0.68	200
1:00	4,300,000	66	39.5	135	560	44	1.010	0.34	200
2:00	—	—	—	—	—	194	1.003	0.12	200
3:00	4,400,000	73	39.5	101	560	295	1.000	0.14	200
4:00	—	—	—	—	—	210	1.000	0.16	200
5:00	4,400,000	69	40.7	101	565	100	1.010	0.14	200

* Given 100 gm. of glucose.

TABLE 6.—*Case No. 201.*—March 27, 1920

Time	Red Cell Vol. %	H g b. %	Plasma		Urine		Fluid Intake cc.
			Sugar mg. per 100 cc.	NaCl. mg. per 100 cc.	Vol. cc.	Glucose %	
7:00	—	—	—	—	—	—	200
8:00	—	—	—	—	75	0	200
9:00 *	46.7	80	125	620	75	0	200
9:30	43.2	73	170	—	—	—	—
10:00	40.5	72	210	615	65	0.54	200
11:00	45.0	74	180	600	310	0.22	200
12:00	48.7	78	130	620	325	0	200
1:00	48.3	77	90	630	325	0	200
2:00	—	—	—	—	300	0	200

* Given 100 gm. of glucose.

TABLE 7.—Case No. 241. — May 1, 1920

Time	R. B. C.	H g b. %	Red Cell Vol. %	Plasma		Blood Urea mg. per 100 cc.	Urine				Fluid Intake cc.
				Sugar mg. per 100 cc.	NaCl. mg. per 100 cc.		Vol. cc.	Sp. Gr.	Sugar %	NaCl. %	
6-7	—	—	—	—	—	—	98	—	—	—	200
7-8*	5,700,000	96	44.6	145	630	28	108	1.031	0	0.96	200
8:30	7,200,000	92	44.0	239	615	32	—	—	—	—	200
9:00	6,300,000	84	42.6	309	660	38	30	—	1.60	0.98	200
10:00	6,000,000	84	42.1	213	640	34	69	1.032	2.86	0.88	200
11:00	6,000,000	96	44.5	182	640	30	48	1.027	0.90	1.24	200
12:00	5,600,000	98	46.8	165	630	30	56	1.025	0.35	1.36	200
1:00	—	—	—	—	—	—	29	—	0	0.88	200
2:00	6,096,000	109	44.2	128	—	28	71	1.019	0	0.72	200
3:00	—	—	—	—	—	—	35	1.021	0	0.60	200
4:00	5,000,000	95	43.2	145	—	—	175	1.010	0	0.38	200
5:00	—	—	—	—	—	—	130	1.007	0	0.28	—

* Given 100 grams of glucose.

TABLE 8.—Case No. 204. — March 30, 1920

Time	R. B. C.	Red Cell Vol. %	H g b. %	Plasma		NaCl. mg. per 100 cc.	Urine		Fluid Intake cc.
				Sugar mg. per 100 cc.	NaCl. mg. per 100 cc.		Vol. cc.	Sugar %	
9:15*	6,600,000	43.2	100	120	633	—	32	0	200
9:45	6,004,000	43.0	91	233	615	—	—	—	—
10:15	6,006,000	38.4	—	269	608	48	48	1.72	200
11:15	6,000,000	41.1	92	169	618	0.42	245	0.42	200
12:15	5,800,000	43.2	92	89	630	—	247	0	200
1:15	—	—	—	—	—	—	230	0	200

* Given 100 grams of glucose.

TABLE 9.—Case No. 224. — April 24, 1920

Time	R. B. C.	H g b. %	Red Cell Vol. %	Plasma		Urine				Fluid Intake c.c.
				NaCl. mg. per 100 cc.	Sugar mg. per 100 cc.	Vol. cc.	Sp. Gr.	NaCl. %	Sugar %	
9:00	—	—	—	—	—	117	—	0.16	0	200
10:00*	7,208,000	92	50	610	103	108	1.006	0.06	0	200
10:30	7,154,000	95	36	610	207	—	—	—	0	200
11:00	7,100,000	98	46	605	142	Unable to void	—	—	—	—
11:30	6,696,000	85	40	575	193	86	1.010	0.08	0.4	200
12:00	7,408,000	85	53	565	145	130	1.005	0.06	0	200
1:00	7,408,000	84	39	590	96	282	1.002	0.06	0	200
2:00	6,208,000	—	—	—	—	215	1.005	—	—	—
3:00	—	—	—	—	—	—	—	—	—	—

* Given 100 grams of glucose.

TABLE 10.—Case No. 263. — June 3, 1920

Time	R. B. C.	Red Cell Vol. %	H g b. %	Plasma		Blood Urea mg. per 100 cc.	Urine				Fluid Intake c.c.
				NaCl. mg. per 100 cc.	Sugar mg. per 100 cc.		Vol. cc.	Sp. Gr.	NaCl. %	Sugar %	
7:40-9:00	—	—	—	—	—	—	33	1.025	1.28	0	200
10:00	—	—	—	—	—	—	43	1.019	1.06	0	200
11:00*	4,864,000	45.7	80	555	131	28	90	1.012	0.54	0	200
11:30	4,680,000	41.6	—	550	237	—	—	—	—	—	—
12:00	4,820,000	43.6	—	565	241	26	45	1.017	0.62	0.20	200
1:00	—	—	—	560	207	33	40	1.022	0.58	0.42	200
2:00	4,800,000	42.6	—	—	174	30	147	1.003	0.14	0	200
3:00	—	—	—	—	—	—	370	1.002	0.04	0	200
4:00	5,000,000	44.8	—	—	109	30	112	1.004	0.12	0	200
5:00	—	—	—	—	—	—	30	—	0.48	0	200
6:00	4,500,000	42.2	—	—	114	—	55	1.013	0.26	0	200

* Given 100 gm. of glucose.

TABLE 11.—Case No. 259. — May 25, 1920

Time	R. B. C.	Red Cell Vol. %	Plasma		Urine				Fluid Intake cc.
			Sugar mg. per 100 cc.	NaCl. mg. per 100 cc.	Vol. cc.	Sp. Gr.	Sugar %	NaCl. %	
7:40	—	—	—	—	112	1.026	—	0.01	200
8:40	—	—	—	—	143	—	—	—	200
9:40	—	—	—	—	305	1.008	0	0.36	200
10:40*	—	—	—	—	270	1.006	0	0.22	200
11:10	5,456,000	39.5	170	590	—	—	—	—	—
11:40	5,440,000	40.4	290	595	240	1.009	0.22	0.32	200
11:40	5,672,000	37.4	414	580	320	1.012	1.18	0.32	200
12:40	5,238,000	37.8	402	590	330	1.014	1.32	0.34	200
1:40	5,632,000	36.1	201	—	295	1.006	0.20	0.12	200
2:40	—	—	—	—	380	1.006	0	0.30	200
3:40	5,856,000	39.5	100	595	245	1.008	0	—	200
4:40	6,040,000	—	96	—	270	1.004	0	—	200
5:40	—	42.6	—	—	—	—	—	—	—

* Given 100 grams of glucose.

TABLE 12.—Case No. 233. — April 30, 1920

Time	Blood Pressure	R. B. C.	H g h. %	Red Cell Vol. %	Plasma			Urine			Fluid Intake cc.
					NaCl. mg. per 100 cc.	Sugar mg. per 100 cc.	CO ₂ Vol. %	Vol. cc.	Sp. Gr.	NaCl. %	
6:30-8:20	—	—	—	—	—	—	—	84	1.028	1.04	200
9:20	138/90	5,860,000	—	—	—	—	—	60	1.027	0.94	200
10:20	127/82	6,000,000	95	48.4	595	126	80.5	85	1.027	0.86	200
10:50	118/62	5,570,000	101	48.3	593	204	80.5	—	—	—	—
11:20	132/78	6,000,000	97	47.5	603	179	—	275	1.006	0.24	200
12:20	127/70	5,600,000	90	47.8	613	120	86.2	180	1.008	0.26	200
1:20	105/63	5,750,000	101	47.8	610	88	84.4	125	1.007	0.40	200
2:20	—	6,000,000	99	—	615	120	—	105	1.007	0.32	200

* Given 100 grams of glucose.

TABLE 13.—Case No. 196. — June 8, 1920

Time	R. B. C.	Red Cell Vol. %	H g h. %	Plasma		Blood Urea mg. per 100 cc.	Urine				Fluid Intake cc.
				NaCl, mg. per 100 cc.	Sugar mg. per 100 cc.		Vol. cc.	Sp. Gr.	NaCl. %	Sugar %	
9:25-10:25	—	—	—	—	—	—	65	1.017	0.96	0	200
11:25*	5,440,000	47.3	106	610	118	26	150	1.008	0.34	0	200
12:25	4,800,000	46.0	113	585	207	20	50	1.016	0.74	0	200
1:25	4,568,000	45.4	102	600	162	20	205	1.006	0.18	0	200
2:25	—	—	—	—	—	—	270	1.000	0.06	0	200
3:25	5,136,000	42.1	102	575	100	—	300	1.005	—	0	200
4:25	—	—	—	—	—	—	Unable	to void	—	—	200
5:25	4,808,000	41.4	96	575	90	—	300	1.004	—	0	200

* Given 100 grams of glucose.

TABLE 14.—Case No. 230. — April, 19, 1920

Time	R. B. C.	H g h. %	Red Cell Vol. %	Plasma		Blood Urea mg. per 100 cc.	Urine			Fluid Intake cc.
				Sugar mg. per 100 cc.	NaCl, mg. per 100 cc.		Vol. cc.	Sp. Gr.	Sugar %	
7:10	—	—	—	—	—	—	—	—	—	200
8:10	—	—	—	—	—	—	26	1.037	1.60	200
9:10	—	—	—	—	—	—	30	1.036	1.59	200
10:10*	6,530,000	91	46	580	20	20	34	1.033	1.59	200
10:40	6,520,000	90	43	555	20	20	93	—	—	—
11:10	5,950,000	88	43	547	365	20	205	1.036	3.00	200
12:10	6,820,000	81	42	553	553	20	205	1.037	6.25	200
1:10	6,220,000	83	43	658	563	20	110	1.043	5.50	200
2:10	5,776,000	84	42	516	565	16	58	1.045	5.00	200
3:10	7,116,000	80	38	439	565	14	800	1.005	—	200
5:10	5,900,000	76	39	329	329	—	—	—	—	—

* Given 100 grams of glucose.

TABLE 15.—Case No. 173.—May 8, 1920

Time	R. B. C.	H g b. %	Red Cell Vol. %	Plasma			Urine				Fluid Intake cc.
				Sugar mg. per 100 cc.	NaCl. mg. per 100 cc.	CO ₂ Vol. %	Vol. cc.	Sp. Gr.	Sugar %	NaCl. %	
6:00	4,780,000	—	—	—	—	—	314	1.013	0.80	0.20	200
7:00	—	—	—	—	—	—	300	1.013	0.28	0.20	200
8:00	—	—	—	—	—	—	93	1.021	1.50	0.30	200
9:00	—	—	—	—	—	—	52	1.023	1.50	0.28	200
10:00*	4,780,000	83	37	366	590	44.3	91	1.016	1.00	0.26	200
10:30	4,950,000	85	37	432	590	46.2	106	—	—	—	200
11:00	5,450,000	79	39	516	600	53.6	84	1.023	1.93	0.18	200
12:00	4,960,000	80	28	592	585	51.9	94	1.025	2.57	0.18	200
1:00	5,550,000	74	40	556	600	—	191	1.014	1.74	0.10	200
2:00	5,840,000	81	36	500	575	—	330	1.009	1.66	0.10	200
3:00	—	—	—	—	—	—	240	1.013	2.16	0.10	200
4:00	4,800,000	75	38	500	595	44.3	205	1.012	1.89	0.12	200
5:00	—	—	—	—	—	—	234	1.010	1.54	0.12	—
6:00	5,000,000	74	31	466	560	50.0	—	—	—	—	—

* Given 50 grams of glucose.

TABLE 16.—Case No. 219.—April 25, 1920

Time	R. B. C.	H g b. %	Red Cell Vol. %	Plasma			Blood Urea mg. per 100 cc.	Urine			Fluid Intake cc.
				NaCl. mg. per 100 cc.	Sugar mg. per 100 cc.	Sugar mg. per 100 cc.		Vol. cc.	Sp. Gr.	Sugar %	
11:00	—	—	—	—	417	—	10	28	1.017	0.65	200
12:00*	5,848,000	107	42.9	620	387	—	10	194	1.017	0.92	200
12:30	5,464,000	92	39.8	590	520	—	10	—	—	—	—
1:00	5,808,000	105	36.2	575	627	—	10	370	1.009	0.71	200
2:00	4,824,000	103	41.9	580	500	—	10	350	1.010	1.25	200
3:00	—	—	—	—	—	—	10	280	1.010	0.90	200
4:00	6,280,000	—	40.2	—	459	—	10	250	1.010	0.61	200

* Given 25 grams of glucose.

TABLE 17. — *Case No. 187.* — March 9, 1920

Time	R. B. C.	H g. h. %	Red Cell Vol. %	Plasma		Urine		Fluid Intake cc.
				Sugar mg. per 100 cc.	NaCl mg. per 100 cc.	Sp. Gr.	NaCl %	
8:30	—	—	—	—	—	105	0.76	200
9:30*	5,500,000	108	32	402	555	45	0.73	200
10:00	5,050,000	60	37	500	545	—	—	—
10:30	3,690,000	58	37	616	545	110	0.48	200
11:30	3,500,000	63	37	483	545	190	0.38	200
12:30	4,400,000	63	38	414	535	150	0.30	200
1:30	—	—	—	—	—	125	0.50	200
2:30	5,600,000	69	37	345	512	810	0.22	200
3:30	—	—	—	—	—	380	0.12	200
4:30	—	—	—	—	—	316	0.18	200

* Given 50 grams of glucose.

TABLE 18. — *Case No. 283.* — May 16, 1920

Time	R. B. C.	H g. h. %	Red Cell Vol. %	Plasma		Urine		Fluid Intake cc.
				Sugar mg. per 100 cc.	NaCl mg. per 100 cc.	Vol. cc.	Sugar %	
6:00	—	—	—	—	—	120	2.25	200
7:00	—	—	—	—	—	130	2.68	200
8:00*	4,030,000	105	33.0	307	460	120	2.11	200
9:00	3,560,000	101	36.2	422	475	150	2.45	200
10:00	4,000,000	100	38.0	453	475	200	2.75	200
11:00	3,976,000	106	34.2	461	435	215	3.15	200
12:00	—	—	—	—	—	180	3.33	200
1:00	4,152,000	102	35.2	414	495	195	2.45	200
2:00	—	—	—	—	—	160	1.029	200
3:00	3,744,000	103	32.6	329	500	115	4.59	200
4:00	—	—	—	—	—	150	3.33	200
							2.75	200

* Given 50 grams of glucose.

TABLE 19.—Case No. 85.—March 26, 1920

Time	R. B. C.	H g. b. %	Red Cell Vol. %	Plasma		Urine Sp. Gr.	Sugar %	Fluid Intake cc.
				Sugar mg. per 100 cc.	NaCl mg. per 100 cc.			
7:30	—	76	—	—	—	1.010	0	200
8:30	5,616,000	76	33.8	123	615	1.010	0	200
9:30	—	76	33.0	198	600	—	—	—
9:30	5,272,000	81	32.5	254	605	1.012	0	200
10:30	5,048,000	83	36.4	210	585	1.009	0	200
11:30	4,904,000	82	34.6	195	600	1.010	0	200
12:30	—	—	—	—	—	1.009	0	200
1:30	6,544,000	80	35.1	161	590	1.008	0	200
2:30	—	—	—	—	—	1.008	0	200
3:30	5,224,000	76	32.0	145	585	1.007	0	200
4:30	—	—	—	—	—	1.009	0	200
5:30	5,272,000	76	30.2	117	590	1.007	0	200

* Given 25 grams of glucose.

TABLE 20.—Case No. 215.—May 17, 1920

Time	R. B. C.	Red Cell Vol. %	H g. b. %	Plasma		Urine Vol. cc.	NaCl %	Fluid Intake cc.
				NaCl mg. per 100 cc.	Sugar mg. per 100 cc.			
6:00	—	—	—	—	—	190	0.32	200
7:00	—	—	—	—	—	310	0.24	200
8:00	—	—	—	—	—	250	0.26	200
9:00	5,400,000	42.7	77	565	133	110	0.62	200
10:00	—	41.3	82	585	125	90	0.94	200
11:00	5,500,000	40.6	81	605	138	90	1.04	200
12:00	5,500,000	42.7	84	605	117	130	0.88	200
1:00	5,400,000	—	—	—	—	190	0.26	200
2:00	—	41.1	80	580	111	295	0.36	200
3:00	5,200,000	—	—	—	—	260	0.28	200
4:00	4,700,000	38.0	84	580	103	230	0.28	200
5:00	4,900,000	38.8	76	575	85	—	—	200
6:00	—	—	—	—	—	—	—	200

* Given 10 grams of NaCl.

TABLE 21.—*Case No. 215.*—June 7, 1920

Time	R. B. C.	H & b. %	Red Cell		Plasma		Urine		Fluid Intake cc.
			Vol. %	NaCl mg. per 100 cc.	Sugar mg. per 100 cc.	Vol. cc.	Sp. Gr.	NaCl. %	
6:00	4,600,000	80	—	—	—	60	—	—	200
7:00	—	—	—	—	—	230	1.011	0.32	200
8:00	—	—	—	—	—	235	1.002	0.12	200
9:00	4,600,000	82	40.9	590	106	215	1.002	0.10	200
10:00	4,600,000	83	41.5	590	105	250	1.004	0.12	200
11:00	4,400,000	83	41.8	575	106	280	1.003	0.18	200
12:00	4,700,000	—	—	—	—	—	1.004	0.14	200
1:00	4,800,000	82	41.6	575	101	130	1.002	0.12	200
2:00	5,000,000	—	—	—	—	120	1.006	0.18	200
3:00	4,760,000	83	41.5	565	105	260	1.004	0.10	200
4:00	4,600,000	—	—	—	—	190	1.005	0.10	200
5:00	—	—	—	—	—	200	1.004	0.12	200

EXPERIMENTAL STUDIES IN DIABETES.

SERIES III. THE PATHOLOGY OF DIABETES

6. PANCREATITIS IN THE ETIOLOGY OF EXPERIMENTAL DIABETES

By FREDERICK M. ALLEN M.D.

*From the Hospital of the Rockefeller Institute for Medical Research,
New York.*

Any review of the past literature of diabetic pathology¹ shows that the condition reported in the great majority of carefully studied human cases has been some degree of so-called pancreatitis, capable of interpretation either as a chronic inflammation or the fibrous repair of former acute inflammatory damage. Attempts to correlate etiologic conditions in clinical and experimental diabetes led to observations which may be grouped under the following five headings: (1) Spontaneous pancreatitis in dogs; (2) Specific influence of infection; (3) Accidental inflammation after partial pancreatectomy; (4) Experiments with pancreatic trauma; (5) Experiments with pancreatic stasis.

1. SPONTANEOUS PANCREATITIS IN DOGS

While the definite relations of artificial experiments give them certain advantages, there are always features of special interest in spontaneous pathologic conditions in animals which resemble those in man. Valuable sources of information are lost through the lack of veterinary practitioners with the scientific spirit and training to investigate and turn to account the interesting material which is open to them. Little has been gained from veterinary literature concerning diabetes beyond the bare fact that the spontaneous disease may rarely occur in dogs, horses and monkeys, generally with some gross pancreatic lesion.

Jorgensen² has published the most recent example of this

kind, which is quoted especially as an interesting analogy to the human cases of diabetes which develop following an acute infection. His patient was a four-year-old black mare, which was brought to him May 14, 1921. The history was that the animal had been ill with influenza four months previously, which had run an atypical course ending in recovery. Some time later marked progressive emaciation was noticed, together with a transitory lameness in all four legs, and an ulcer the size of a silver dollar on the left half of the mammary gland. A thorough general examination showed marked glycosuria and lipemia, though no quantitative analyses were performed. It was considered impossible to place a horse on a carbohydrate-free diet, and a fatal prognosis was given. Death occurred July 23, and an autopsy was performed the same day. The heart was enlarged and showed lesions of an old endocarditis. The spleen contained a well-capsulated abscess, the contents of which were inspissated and partially absorbed. The stomach and intestines were normal with the exception of marked congestion and ulceration of the diverticulum duodeni, involving in particular the hepatic duct. The entire right lobe of the liver had undergone atrophic sclerosis and contained the remnants of a large abscess almost completely absorbed; the middle lobe was congested, while the left lobe appeared normal. The entire hepatic duct was congested and contained two small ulcers from which streptococci and colon bacilli were isolated. "The pancreas had undergone an extensive degenerative process of a colloid variety and appeared to have been the seat of several minute abscesses. The duct was somewhat thickened by congestion. The kidneys both showed lesions of a slight interstitial nephritis." The deduction of this veterinary writer is instructive. "Conclusions of my diagnosis made antemortem remained unchanged, except as it concerned the cause of the glycosuria, which the autopsy showed to be of a pancreatic variety due to degenerative processes brought on by an atypical infection in the form of influenza."

Since the tremendous increase in the apparent incidence of human diabetes with better diagnostic methods has proved the unreliability of the older statistics, as pointed out in Joslin's text-book, the uncertainty of any existing statistics concerning dogs will be apparent to anyone who considers how

seldom a case in a dog would be likely to be diagnosed. The writer has examined the urines of over a thousand dogs without ever finding sugar, but the same experience might be possible with a thousand men chosen at random. The case-report by Krumbhaar³ possesses unique importance, because of the following features: (1) though some pancreatitis was present, there was no extensive sclerosis; the diabetes was not due to duct obstruction or any gross destructive process, but may possibly have been connected somehow with the tumor which was present; (2) diabetes occurred in this dog, just as in some human cases, with an abundance of normal-appearing pancreatic tissue present, both acini and islands; (3) there was hydropic vacuolation of some island cells, as found in the experimental diabetes of dogs and in human cases.

Pancreatitis has been reported occasionally in several animal species, and is evidently more common than diabetes. The writer has observed the pancreas at operation or autopsy in more than a thousand dogs of which the urinary record was known. Microscopic examinations were made in over four hundred cases, including all in which there was any suspicion of abnormality. Pancreatitis, in the form of various grades of induration, fibrosis and atrophy, was found in 8 cases. The fibrosis was invariably interlobular, and without demonstrated cause. Five of the animals, examined at autopsy, require no special mention except that they were all senile; four of them were obese, and the fifth had an excess of peritoneal fat out of all proportion to that on the body. In four the pancreas was merely firm and nodular, not below the average in size or weight, and only moderately fibrosed microscopically. In one dog weighing 9.6 kgm. the pancreas weighed only 12 gm. and the gross and microscopic appearances of atrophy and fibrosis corresponded. In one dog there was also marked interstitial nephritis.

In the other three animals, observations were made during life as follows.

Dog D4-33. — Female; black shaggy mongrel aged 7 or 8 years; weight 19.6 kgm.; very fat and sluggish. Oct. 20, 1916, removal of pancreatic tissue weighing 21.7 gm. Remnant about main duct estimated at 1.85 gm. (1/13). The pancreas was distinctly firm and nodular, and microscopically showed moderate interlobular fibrosis, but was not apparently atrophied, the disproportion between its weight and the body weight being due to obesity. On lung diet there was

glycosuria ranging between 2 and 5 per cent up to death on Nov. 5. The whole course corresponded to that in a normal dog, without any difference attributable to the pancreatitis.

Dog D4-66. — Male; long-haired yellow mongrel; age 4 or 5 years; obese; weight 24.5 kgm. Dec. 21, 1916, operation showed the pancreas to be markedly but irregularly atrophic; segments several centimeters in length were shrunk to a fibrous band no larger than a goose quill, while alternating with them were full-sized segments of apparently normal issue. The splenic and uncinat process, weighing together 19.85 gm., were removed, leaving the body of the pancreas, which because of atrophy was estimated at only 5 gm. The dog thrived after the operation; the healthier portions of the remnant apparently furnished sufficient digestive juice to prevent malnutrition. Glycosuria remained absent on bread and soup diet with increasing additions of glucose up to 300 gm. daily. The same condition continued after removal of 0.75 gm. additional pancreatic tissue on Jan. 10. The dog was killed Jan. 24, and nothing noteworthy found except the same marked interacinar pancreatitis. The experiment thus failed to demonstrate any unusual tendency to diabetes or hydropic degeneration in pancreatic sclerosis of a type which spared the islands.

Dog B2-67. — Female; black and white shaggy mongrel; age 5 or 6 years; thin but lively; weight 12.4 kgm. May 26, 1914, operation showed the pancreas uniformly shrunk to a very hard, nodular band surrounding the duct, so that the total weight was estimated at about 6 gm., in a dog which if normally nourished would have weighed fully 18 kgm. The tip of the splenic process, weighing 0.7 gm., was removed as a specimen. The dog was then kept under observation for the possible spontaneous development of diabetes. The diet was bread and soup, on which the animal was able to hold weight by eating huge quantities. The feces were bulky but formed.

June 22, a series of tests of food utilization were begun, by feeding cooked beef-lung for the first period and raw pancreas for the second. The results concern the present topic only in that they showed extremely poor digestion and absorption, not appreciably better for the pancreas than for the lung, and not remedied by mincing either lung or pancreas. There was also copious foul diarrhea, which could not be checked by bonemeal. The animal lost weight down to 8.4 kgm., so that on July 10 the test had to be stopped. Change to bread and soup then raised the weight to 12 kgm. by July 30.

July 30, the dog was given 48 gm. Merck glucose (4 gm. per kilo on 12 kgm. weight) in 30% solution by stomach tube. In the following 2 hours, there was glycosuria of only 0.1% in 10 cc. urine, and no sugar excretion thereafter.

The weight reached its highest point of 13 kgm. on Oct. 16. Thereafter it gradually fell, notwithstanding the occasional feeding of milk in addition to the bread and soup. Nov. 9, at a weight of 11.4 kgm. the dog was given 48 gm. glucose in 30% solution subcutaneously with the result of only a bare trace of sugar in 25 cc. urine.

By May 24, 1915, the weight had fallen to 9.2 kgm. The dog, though emaciated and weak, was always lively and voracious. Death occurred unexpectedly from unknown cause on May 28. At autopsy, the large intestine was remarkably enlarged and distended, perhaps on account of the huge amounts of soft fermenting feces. The pancreas appeared even more atrophic than before, and weighed only 4.3 gm. Its duct was fully patent, and no cause for the sclerosis was found. The other viscera were negative.

The microscopic picture both at operation and at autopsy was interlobular pancreatitis of extreme degree; but, as shown in Fig. 1, the islands were saved by their interior position until the entire lobule was destroyed. Malnutrition was another important factor in preventing diabetes in such a case.

2. SPECIFIC INFLUENCE OF INFECTION

A number of experiences with infections were described in papers 5 and 6 of Series II.⁴ The aggravating influence upon an existing diabetes was much less marked than in human cases, and the accompanying cachexia often served instead to suppress glycosuria. No actual production of diabetes or the characteristic pancreatic lesions was found in a long list of acute and chronic infections, including distemper, rabies, pneumonia, and various forms of sepsis, even when the pancreas remnant was bathed in the pus of a peritoneal abscess.

There were opportunities of observing the effects of distant foci, when natural or experimental causes happened to give rise to localized collections of pus in the subcutis, pleura or peritoneum, which were sometimes carried for more than a year without symptoms, and sometimes led to death through chronic intoxication. Neither inflammatory nor degenerative changes were found in the pancreas in any such cases; in particular, neither fibrosis nor "atrophy" of islands.

In several experiments with trauma or circulatory stasis of the pancreas, of the kind described below, the necrosis of portions of tissue was followed by infection, so that the pancreas remnant became riddled with small abscesses. Some of these animals remained free from diabetes; others became diabetic apparently in direct consequence of the infection; but, aside from the factor of cachexia, the difference seemed to depend entirely upon the quantitative destruction by necrosis or inflammation. The islands seemed not to be spe-

cifically destroyed or spared; also there was no indication of a functional injury giving rise to diabetes.

As far as experimental conditions were concerned, there was no evidence of any specific influence of infection upon the pancreas or its islands, or any greater tendency to diabetes than from an equal degree of pancreatic damage produced by some other agency.

3. ACCIDENTAL INFLAMMATION AFTER PARTIAL PANCREATECTOMY

A. *Acute pancreatitis.*

When the abdomen is opened several hours to several days after a partial pancreatectomy, the remnant is found covered by the omentum which was draped around it at operation, and which is now adherent, inflamed, and dotted with fat necroses. The remnant itself is more or less swollen and turgid, whiter than normal on the uninjured surfaces and hemorrhagic where cut or bruised. Microscopically, true inflammation is limited to the immediate vicinity of the cut surfaces. The interior may be normal, or especially with a small remnant there are edema, hemorrhages and leukocytic infiltrations of the interlobular septa, but no disturbance inside the lobules. Such changes gradually subside leaving no trace. In occasional instances more profound alterations occur, which may be indistinctly separated into two groups.

In one form a riot of inflammation predominates. The tissue is infiltrated in all directions with polymorphonuclear and endothelial leukocytes, lymphocytes, young fibrous tissue and red blood cells. The acini may at first show small necroses, but later are found in all stages of involution and degeneration. The islands are sometimes spared by their central position if the process is chiefly interlobular, but there are extreme instances in which lobules are indistinguishable and islands cannot be found, being either destroyed or unrecognizable amid the confusion. In the later stages fibrosis predominates; active inflammation ceases, and the degenerative changes in the parenchyma are attributable to strangulation by the fibrous tissue (*Figs. 2 and 3*).

The other form apparently takes its origin in a similar

welter of inflammation, but is characterized by peculiar epithelial formations. Amid the inflammatory disorganization may be found a profusion of poorly differentiated cells, which are evidently not all derived from involution of the old epithelium but are probably a new proliferation. Fibrosis is relatively slight, and as the inflammation subsides atypical staining becomes a striking feature in the parenchyma. Some areas or lobules are strictly normal, while adjoining areas stand out in sharp contrast by reason of their very pale staining and the apparent lack of basophilic material in the acini. Opposed to the supposition of a necrotic or degenerative change is the healthy appearance of all these cells, in the form of clear-cut outlines, sharply differentiated nuclei and nucleoli, abundance of pale-staining zymogen in the acini, and distinct though pale granulation in the islands. These appearances have been specially prominent in some hypertrophic remnants, and the impression has been gained that they represent new-formed tissue. No positive judgment can be reached without high-power studies of serial sections of tissue at the different stages, to search for mitoses in the various types of cells and follow the course of the hyperplasia. Such a study was impossible chiefly because of lack of time, but partly because of the rarity of such changes and the inability to predict them in any given case. The probability of new formation of islands in such pancreas remnants (*Fig. 4*) has been previously mentioned.⁵

B. Chronic pancreatitis

After partial pancreatectomy in the great majority of cases the effects of trauma subside leaving the parenchyma normal except for a narrow zone of scar tissue bordering the cut surface, and the assimilative power remains stationary in such a manner as to permit pure observations on functional influences, as described in Series I and II. In the minority of cases with more extensive scarring, this shows no tendency to advance with time and leaves the assimilation unaffected. Sandmeyer's operation, which involves duct occlusion, naturally leads to complete sclerosis of the gland and hopeless diabetes. Otherwise a true chronic fibrosis with corresponding progressive deterioration of tolerance is a rarity.

Dog D4-14.—Female; fox terrier mongrel; white and yellow; age 3 years; fat; weight 9 kgm. July 13, 1916, removal of splenic process and most of body of pancreas, weighing 10.7 gm., leaving the uncinate process and tissue about the main duct, estimated at 8.6 gm. The dog was unwell for about a week after operation. Glycosuria then remained absent on bread and soup and other diets. On Sept. 14 the plasma sugar was 0.130%, and on Sept. 18 0.127%, the slight elevation being presumably due to the fact that the dog was excitable and not accustomed to bleeding. Weight continued to be lost, down to 5.7 kgm. on Oct. 5. Nevertheless the plasma sugar on this date was 0.164%, on a carbohydrate-free diet of lung and suet. Oct 19, after further loss of weight to 5 kilos, the plasma sugar before feeding was 0.132%, and 5 hours after a protein-fat meal 0.152%. By Nov. 18 the dog had lost weight to 4.7 kgm., owing to dislike of meat and fatty indigestion, and a change was thereafter made to bread and milk, which was eaten well but caused slight glycosuria. This became heavy (up to 4.8%) on the following days. Dec. 5, the plasma sugar was 0.097% before feeding, but rose to 0.384% during the carbohydrate digestion. Though weight had been regained by this time up to 5.25 kgm., a peculiar ataxia developed, also large superficial ulcers of gangrenous character. On account of the latter the dog was killed Oct. 11, when the glycosuria was 5.3% in 280 cc. urine, and the plasma sugar without food was 0.218%.

The pancreas remnant was small, smooth, glistening, almost without lobulation, soft and easy to cut, not apparently sclerotic, but weighed only 3.9 gm. The other viscera appeared normal.

Microscopically, the pancreas showed slight diffuse fibrosis and irregularities in size, shape and fullness of the acini. Islands were variable in number and size but on the whole fairly abundant. No gross destructive process was evident to account for the gradual development of diabetes. The majority of the island cells were in various stages of vacuolation. (See Fig. 5.).

Dog F6-16.—Male; fox terrier; black and white; age 3 or 4 years; medium nutrition; weight 8.7 kgm. Dec. 19, 1919, removal of splenic process and most of body of pancreas, weighing 13.7 gm., leaving uncinate process and tissue about main duct estimated at 11 gm. The pancreas was normal to gross and microscopic examination. Glycosuria remained absent on bread diet.

Dec. 21, the abdomen was opened by removing sutures from the recent wound, and 2.5 gm. of inflamed, succulent pancreatic tissue was removed. Microscopically, the swollen septa were markedly infiltrated with red blood cells and leukocytes, but there was only slight marginal invasion of the lobules. Both acini and islands were pale and showed appearances of edema, but this was easily distinguished from hydropic degeneration. Glycosuria was absent as before.

Dec. 31, the plasma sugar without food was found to be 0.17%. The abdomen was then opened by a new incision, and 1 gm. of tissue removed from the pancreas remnant, which appeared only slightly inflamed. Microscopically, the acute changes were less than before,

but parts of the parenchyma were invaded by round cells and young fibrous tissue. The acini were irregular in size and form. Islands were scarce in some areas, but fairly abundant as a rule. They were not directly invaded by fibrosis, but probable early hydropic changes were found in a few cells.

Sporadic glycosuria occurred on bread diet as follows: 0.8% in 200 cc. urine on Jan. 3; 2.2% in 260 cc. urine on Jan. 8; 1.5% in 420 cc. urine on Jan. 17. The urine otherwise was normal up to Jan. 23. The dog was thriving at a weight of 7.5 kgm. The plasma sugar before feeding on Jan. 5 was 0.182%. On Jan. 15 it was 0.139% just before feeding at 11 A.M., and 0.167% at 5 P.M. Jan. 23, glycosuria of 4% in 700 cc. urine appeared suddenly, diminished gradually on the following days to a slight reaction on Jan. 27 and 28, then became heavy again. Jan. 30, the plasma sugar at the height of digestion was 0.475%.

During Jan. 31, without food, glycosuria ceased. The abdomen was then opened, and the pancreas remnant found atrophied to half the original size, but still larger than the size ordinarily required to prevent diabetes. Three bits of tissue, weighing together 0.4 gm., were removed for examination. One of these consisted of degenerating areas of parenchyma amid fibrous tissue, without discoverable islands. In the other two the lobules were invaded only about their periphery; the acini were fairly regular and well filled and stained normally; islands were scarce and small but free from fibrosis, and their diminution might have been due to the marked hydropic changes in progress.

Glycosuria returned on one day of bread feeding, then was absent on a diet of 300 gm. lung and 100 gm. suet till Feb. 10, when a heavy reaction appeared. After a day of fasting it was absent on 200 gm. lung and 100 gm. suet till Feb. 17, when it again became heavy. The animal then gradually became unable to remain sugar free on 100 gm. lung and 100 gm. suet, and the weight diminished to 4.5 kilos. The animal was killed on March 3, when moribund from extreme weakness. The pancreas remnant was atrophic, harder than normal, and weighed only 2.5 gm. The other organs were negative.

Microscopically, some sections consisted of degenerating parenchyma engulfed in fibrous tissue. The majority showed fibrosis which was chiefly interlobular but also interacinar. The acini were mostly distorted and in various states ranging from normal zymogen content to complete involution. Islands were scarce and in the last stages of hydropic degeneration, but not fibrosis. Only small clumps of normal appearing alpha cells and maximally vacuolated beta cells remained. There was no vacuolation of ducts. The ganglia and nerve fibers appeared to be undergoing strangulation by scar tissue.

C. Diabetes with exceptionally large pancreas remnants.

Dog B2-46.—Male; yellow mongrel; age 4 years; thin but strong; weight 22 kgm. March 26, 1914, removal of pancreatic tissue weighing 32.5 gm. Remnant about main duct estimated at 5.9 gm. (1/6-1/7). Glycosuria was absent on fasting up to March 30, then immediately

became heavy on bread and soup diet. The asthenia and cachexia were as marked as in any totally depancreatized animal. Also superficial ulcers developed in different parts of the body and extended rapidly, apparently representing a true diabetic gangrene. Change to meat diet on April 8 brought no improvement. April 13, a burrowing ulcer over one hip opened a large blood vessel and the dog bled to death. The autopsy was negative except for emaciation. The pancreas remnant weighed 11.5 gm., and was soft, lobulated and normal in appearance. Microscopically there was slight diffuse pancreatitis, in the form of fibrous strands and round cells, but not to an extent threatening the vitality of either acini or islands. Islands were noticeably scarce and small, but not sufficiently so for explanation of the diabetes by a simple quantitative reduction. A minority of island cells showed slight to moderate hydropic changes.

Dog E5-16. — Female; yellow mongrel; age 4 years; good condition; weight 18 kgm. Pancreatic tissue was removed in two operations, April 3 and 25, 1917, leaving a remnant about the main duct estimated at 6.75 gm. or 1/5 of the gland. Glycosuria was maintained at first by bread diet with 100 gm. glucose, later by mixed diets of bread, lung and suet. Death occurred on July 10 after marked lipemia, acidosis and prostration, probably an atypical coma. The general autopsy was negative except for fatty liver and congestion and Armanni vacuolation in the kidneys; also the hypophysis was intensely congested and its eosinophile cells were strikingly numerous and prominent. The pancreas remnant weighed 9 gm. and seemed entirely normal in gross structure. Microscopically there was slight diffuse pancreatitis in the form of fine fibrous strands spread almost uniformly between the acini. The acini were irregular in shape and size, but well filled with zymogen and otherwise healthy in appearance. Islands were very scarce and small in some sections, large and numerous in others, entirely free from fibrosis, but with maximal vacuolation of a majority of cells. The indications were plain that diabetes had occurred with an abundance of islands, and that their reduction in some areas was due to the hydropic process and not to fibrosis.

Dog B2-81. — Male; yellow mongrel; age 3 years; good condition; weight 17.5 kgm. Nov. 17, 1914, removal of pancreatic tissue weighing 31.4 gm. Remnant about main duct estimated at 8.72 gm. (slightly over 1/5). Glycosuria resulted promptly from bread feeding. The dog was then kept in a border-line condition, so that the tolerance was between 100 and 200 gm. of dry bread, rice or oatmeal, until accidental death on June 26, 1915. The general autopsy was negative. The pancreas remnant, normal in appearance and consistency, weighed 8.1 gm. Microscopically it was normal except for trivial increase of fibrous tissue, which might have passed unnoticed except for special search. Islands were moderate in number and size and normal in appearance.

Dog E5-39. — Male; St. Bernard; age 6 or 7 years; slightly thin; weight 36 kgm. May 14, 1917, removal of pancreatic tissue weighing 48.7 gm. Remnant about main duct estimated at 10.2 gm. (1/6). Glycos-

uria was absent on bread diet up to May 18, then present with addition of 200 gm. glucose daily, then after May 22 on bread alone, and after May 25 on lung and suet. Severe diabetes and moderate acidosis then continued up to accidental death on June 12. The pancreas remnant, weighing 13.2 gm., was normal grossly and microscopically except for marked vacuolation of a majority of island cells. There was no sign of inflammation or fibrosis; the acini were regular and well filled, and islands were strikingly large and numerous.

Dog C3-20 was mentioned in paper 2 of series II⁶. June 24, 1915, 40.4 gm. of pancreatic tissue was removed, leaving a remnant estimated at 11.5 gm. Additional tissue was removed as follows: July 16, 2.2 gm.; July 30, 1.2 gm.; Aug. 16, 0.6 gm.; Nov. 1, 1.4 gm. Potential diabetes was present after Aug. 16, and the dog was used to show the onset of symptoms with gain of weight. Death occurred from hernia of the operative wound on Nov. 3, when the pancreas remnant was found to weigh 14.2 gm. The tissue examined on all the above occasions was normal, except for hydrops in some island cells at autopsy, and occasional patches of slight fibrosis.

Dogs B2-80 and B2-02 were described in paper 2 of Series I⁷. The former became diabetic with a pancreas remnant estimated at 7.1 gm., or between 1/4 and 1/5 of the pancreas. Apparently all beta cells were lost by hydropic degeneration during the course of diabetes leading to death in coma. The pancreas remnant at autopsy weighed 13.5 gm., and was entirely free from inflammation or fibrosis. The latter dog become diabetic after a series of operations which left approximately 1/4 of the pancreas. The pancreas remnant at autopsy was normal in gross appearance. Microscopically, in addition to slight hydropic changes corresponding to the latent diabetes, there were found scarcity and smallness of islands and occasional slight inter-acinar fibrosis.

Dog B2-38.—Female; brown and white bull terrier mongrel; age 2 years; lean, muscular and strong; weight 12.3 kgm. Jan. 27, 1914, removal of pancreatic tissue weighing 17.8 gm. Remnant about main duct estimated at 3.6 gm. (1/6). Owing to some operative difficulties, there was unusual trauma of the remnant, which might be expected to cause inflammation. On bread and soup diet glycosuria was slight or absent up to Feb. 12, when it suddenly became heavy. It continued so after change to meat diet on Feb. 19. The diabetes then ran a rapid course to death in extreme emaciation and cachexia on April 3. The general autopsy was negative. The pancreas remnant, normal in appearance and consistency, weighed 5.3 gm. Microscopically, the acini were normal but nearly empty, so that the actual hypertrophy was probably greater than indicated by the weight. The islands were in the final disappearing stage of hydropic degeneration. No fibrosis or signs of inflammation were found. If pancreatitis following the rough operation was responsible for the onset of diabetes on Feb. 12, it had evidently cleared up completely in the intervening period.

Dog C3-84.—Female; mongrel bull terrier; brindle and white; age

9 months; medium nutrition; weight 10.25 kgm. April 20, 1916, removal of pancreatic tissue weighing 27.8 gm. Remnant about main duct estimated at 3.1 gm. (1/10). Glycosuria was transitory on bread diet alone or with addition of 100 gm. glucose, which was all the dog would take. May 25, operation showed the pancreas remnant greatly hypertrophied. 2.25 gm. of tissue was removed, leaving a remnant estimated at about 5 gm. Diabetes resulted, and the dog was later sent to another laboratory. The tissue removed on May 25 was free from inflammation or fibrosis. Islands were scarce in some areas, numerous in others; nearly all were small, but otherwise they appeared normal like the acini.

This and similar records which might be given illustrate the hypertrophy of a small remnant which is successful in preventing diabetes. Other examples of hypertrophy were formerly given⁸, which raised the question of the functional valency of the islands present. The problem is simplest when a scarcity of islands is found, in the absence of hydropic degeneration. If the original remnant was small, there is the possibility that the hyperplasia was limited to the acinar tissue; while if the original remnant was large, it may be assumed that the islands were destroyed by inflammation. When diabetes occurs with a large remnant containing an abundance of islands, it must be concluded either that the old islands have suffered injury in their function from some cause (presumably the inflammation), or that the old islands have been destroyed and that the new islands are inferior in functional capacity. Any supposition that the new islands, which appear perfectly normal under routine stains, may be composed chiefly of alpha cells is positively excluded by the following two facts: first, stains by Bensley's method in certain such cases have shown the usual preponderance of beta cells and fewness of alpha cells; second, the islands in these large remnants are subject to hydropic degeneration in precisely the usual manner. As a general rule, the new-formed tissue possesses distinct functional power, as shown by a gain of tolerance (unless hydropic degeneration is employed by means of over-feeding to damage the islands during the process of hypertrophy). But this functional power is very seldom normal, as shown by the fact (cf. dog C3-84 above and dogs B2-63 and C3-27 in paper 2 of Series I⁹) that the removal of very little tissue suffices to restore the diabetes, though the operation still leaves a large remnant full of normal-appearing islands. These observations seemed highly important

in connection with the etiology of human diabetes, for they showed that certain exceptional cases in dogs reproduced the most puzzling features of the pathology of human cases; namely, the occurrence of diabetes in the presence of large masses of pancreatic tissue, which may sometimes be poor and sometimes rich in islands.

4. EXPERIMENTS WITH PANCREATIC TRAUMA

From comparisons of cases such as described, it finally seemed probable that they represented variations of the same process; namely, that the traumatic inflammation was sometimes accompanied by necrosis and followed by fibrosis, or again served chiefly as a stimulus to epithelial proliferation; also that the islands might be either destroyed or functionally damaged in such inflammation. The attempt was therefore made to reproduce these conditions intentionally. Since infection, which is the most probable agent in human cases, seems to lack any strictly specific influence as mentioned under section 2 above, recourse was had to the more easily controllable agency of aseptic inflammation.

The first method tried was merely an exaggerated operative trauma, in the form of squeezing and crushing of the pancreas remnant. The remnant being surrounded with gauze to prevent slipping and tearing, pressure was made intermittently with the fingers for perhaps ten minutes, squeezing out considerable fluid and bruising the tissue as deeply and uniformly as possible without causing necrosis of any large portion. If such necrosis occurs the animal dies, while if the trauma is insufficient there is no diabetes. These irregularities made the method an uncertain one, but some of the more successful results are given below.

Dog C3-78.—Female mongrel; white and brown; age 4 or 5 years; slightly obese; weight 17.25 kgm. April 13, 1916, removal of pancreatic tissue weighing 24.1 gm., leaving remnant about main duct estimated at 4.8 gm. (1/6). Diabetes was absent on bread and glucose feeding. April 26, a bit of pancreatic tissue was removed as a specimen, and the remnant traumatized by pressure with fingers. The tissue removed at both these operations was microscopically normal.

The urine from operation to the morning of April 27 was 190 cc., with 4.55% sugar. This glycosuria fell to traces on bread diet, but became heavy with addition of glucose up to 150 gm. daily. Beginning

May 8 the diet was changed to beef lung. The glycosuria gradually diminished and was absent on May 14, but on May 15 the plasma sugar was still 0.162%. Various tests were then performed, with continuance of hyperglycemia and glycosuria even on fat feeding or fasting. Accidental death occurred May 23, when the weight was 12.25 kgm.

Autopsy was negative except for the pancreas remnant, which was not obviously sclerosed but weighed only 2.5 gm. Microscopically there was diffuse interacinar fibrosis, apparently quiescent, without important destruction of parenchyma or round-cell invasion. The acini, though often irregular in form, were well filled with zymogen and not degenerating. Islands were probably slightly reduced in number and size but not fibrosed. Hydropic changes were moderate, but the most interesting were possible appearances of "atrophy" in certain islands, which however could not be vouched for as identical with the familiar condition in human cases.

Dog C3-83.—Male; Dachshund; age 2 years; medium nutrition; weight 9.25 kgm. April 20, 1916, removal of pancreatic tissue weighing 21.1 gm. Remnant about main duct estimated at 4.3 gm. (1/6). Diabetes could not be induced by bread and glucose feeding.

May 19, the pancreas remnant was traumatized by crushing between fingers. Fragments weighing 0.3 gm. were broken off in this process, and proved to be normal microscopically.

Heavy glycosuria followed on bread diet, but ceased whenever a change was made to meat. The dog was kept in a border-line condition by alternations of diet, and showed no progressive tendency in the diabetes. Finally heavy glycosuria was allowed to continue and the dog died in cachexia Oct. 13, at a weight of 6.3 kgm.

The pancreas remnant was normal in appearance, consistency and lobulation, and weighed 4.6 gm. Microscopically, islands were found diminished by reason of extensive hydropic degeneration, but the tissue was otherwise strictly normal and free from inflammation or fibrosis. The important feature of the experiment therefore was that diabetes had been produced by an acute traumatic inflammation, and had continued to a fatal end after the inflammation had subsided leaving no visible trace.

Dog C3-94.—Male; French bulldog mongrel; age 4 or 5 years; good condition; weight 14.6 kgm. May 26, 1916, removal of splenic and uncinat processes, weighing 31.3 gm., leaving the entire body of the pancreas, estimated at 12.8 gm. (1/3-1/4). The remnant was then traumatized by crushing between the fingers. The tissue removed was microscopically normal.

Heavy glycosuria was kept up by bread and glucose diet, but ceased when bread was fed alone and tended gradually to diminish. June 10, with glycosuria still present, 0.2 gm. of pancreatic tissue was removed for examination. The pancreas remnant in this operation seemed as long as before but was distinctly thinner and firmer, though not nodular or deformed. The tissue removed showed moderate diffuse

fibrosis, in the form of irregular bands invading the lobules. The majority of the acini were well filled with zymogen and normal except for some distortion, but some had evidently been destroyed and others were in various stages of involution. Islands were scarce in some fields, abundant in others; they sometimes appeared distorted by neighboring fibrous tissue but their interior was never invaded.

Glycosuria continued to diminish till it ceased with failure of appetite for sugar on June 20. June 23 the abdomen was again opened and the pancreas remnant found approximately as before, though some parts seemed softer and less atrophic. Trauma by crushing was repeated, and also a tiny specimen of 0.2 gm. was removed from the atrophic portion. Microscopically, fibrosis was present and hydropic changes absent as before.

Glycosuria was absent up to the feeding of bread and milk with 150 gm. glucose on June 25, and then amounted to 5.9% in 520 cc. urine. It remained heavy on bread diet after the glucose was gradually withdrawn, also on lung diet, but ceased with 2 days of fasting. It returned immediately on lung and suet diet, and acidosis gradually developed, aided by the dog's good digestion of fat. Coma failed to ensue, however, and the dog was killed Aug. 29 when in extreme cachexia at a weight of 8.5 kgm.

The pancreas remnant contained one shrivelled area, but otherwise had lost its atrophic appearance and was soft and normally lobulated. Its weight was 9 gm. Microscopically, marked fibrosis was limited to the atrophic area. The remainder might have passed as normal except for slight thickening of some fibrous trabeculae and irregularities of lobules and acini. Only small remains of islands in the last stages of hydropic degeneration could be found. In view of the history, the most interesting feature was the resemblance to the pathologic findings in many human cases.

Dog D4-49. — Male; hunting dog mongrel; age 3 years; medium nutrition; weight 24 kgm. Nov. 24, 1916, removal of both processes of pancreas, weighing 28.5 gm., leaving the body of the gland estimated at 15 gm. (about 1/3). Diabetes remained absent.

Dec. 7, the remnant was traumatized by crushing between the fingers. The dog was unwell for more than a week following operation, but gradually regained spirits and appetite. Glycosuria began Dec. 12 with the eating of the first bread and soup, and continued heavy thereafter (up to 6.5%). It still continued heavy after change to protein-fat diet on Dec. 22. Moderate lipemia ensued, but only slight acidosis. After being used for a few incidental tests, the dog died Jan. 11 (1917) in exreme cachexia at a weight of 13 kgm.

The pancreas remnant consisted chiefly of a nearly normal but slightly hardened portion about the main duct, and atrophic nodular tissue over the remaining area of the corpus pancreatis. The total weight was 7 gm. Aside from fatty liver and the usual Armanni vacuolation in the kidneys, the autopsy was otherwise negative. The atrophic portions of the pancreas were microscopically fibrosed as suggested by the gross appearance, the smaller nests of parenchyma

undergoing involution, though many larger areas persisted little changed amid the scar tissue. The portion which was nearly normal in gross was found surprisingly little changed microscopically. Only the thickening of occasional fibrous trabeculae remained as evidence of former injury. The acini were normal in form and staining and well filled with zymogen. Only disappearing remains of islands in the last stages of hydropic degeneration were present, but there was no fibrosis or sign of a destructive process other than the hydropic change.

In this case different portions of the pancreas evidently reacted differently, probably because of different degrees of injury. One portion suffered fibrosis and atrophy, while in the other either repair or regeneration restored a nearly normal appearance of the tissue. The diabetes which began in the acute inflammatory period was permanent nevertheless.

Dog D4-95. — Male; Dalmatian; old; well nourished; weight 23.4 kgm. Feb. 8, 1917, 31.7 gm. of pancreatic tissue was removed, and 24.3 gm. on April 3, leaving a remnant estimated at 11.5 gm. or 1/6 of the pancreas. This remnant at the second operation was traumatized by pressure, and glycosuria began after the feeding of bread and milk on April 4. It continued heavy with a change to lung and suet diet on April 6, and heavy acetone reactions gradually developed. Death occurred in an operation on April 20, when the dog was in good strength at a weight of 20.6 kgm.

The pancreas remnant was imbedded in a mass of omental adhesions, was markedly enlarged and inflamed, and contained one small abscess, the pus from which showed numerous cocci and bacilli. After emptying the abscess and trimming away all adhesions, the weight still reached the surprising figure of 38.1 gm. Microscopically, there was the same welter of inflammation, degeneration and regeneration as described under section 3. One extreme of the process was represented by sections in which degenerating remains of parenchyma were being swallowed up in masses of fibrous tissue and leukocytes. The opposite extreme appeared in sections showing only occasional slight invasions of round cells or fibrous tissue, chiefly along the natural septa, while the acini were irregular in form and fullness but otherwise normal, with nothing to indicate whether they were old or new-formed. The majority of slides presented all possible mixtures and gradations between these extremes. No islands could be positively identified anywhere. Occasional tiny clumps of cells in the better portions of parenchyma were probably surviving alpha cells. Vacuolated duct cells were a very prominent feature, in the form of ducts, cords and cells heaps. It could therefore be inferred that whatever beta cells survived the inflammation had been completely lost through hydropic degeneration. The nerve ganglia appeared normal as usual, except when directly included in an inflammatory area, in which cases there were invasion and destruction.

In this animal a genuine marked hypertrophy of the remnant seemed probable, in addition to any temporary swelling.

These experiments confirmed the supposition that traumatic inflammation might lead to various end states of atrophy or hypertrophy having diabetes as their common feature, due to organic destruction or functional injury of the islands. It was originally feared that illness during the period of acute pancreatitis would prevent the animals from eating and thus interfere with the development of diabetes. In actual experience illness or anorexia was rare. Extensive necrosis or infection was necessarily fatal, while minor or circumscribed forms of the same, which might end in recovery, were doubtless responsible for the temporary malaise in exceptional animals, such as dog D4-95. Ordinarily, trauma which produced intense inflammation and a sprinkling of small necroses gave rise to no clinical symptoms whatever. The animals were eager for food and drink within a few hours after the operation, and neither fever, indigestion nor impairment of spirits gave any indication of the serious trouble in the pancreas.

5. EXPERIMENTS WITH PANCREATIC STASIS

The above method of mechanical trauma was so uncertain and failures were so numerous that some more accurately controllable method was desirable, both for convenience in this research and to facilitate repetition by others. Trial was therefore made of circulatory stasis, with the idea that this might directly injure the pancreatic cells in structure or function and also indirectly produce inflammation. Clamps with rubber covered jaws, the same as used for intestinal operations, were applied to the pancreatic vessels so as to shut off circulation completely for definite periods of time. The pancreatic tissue took on a dull and dead appearance, and then flushed pink on removal of the clamps. This method produced diabetes with fewer failures. Explanations are necessary concerning the duration of stasis and the preparation of the pancreas remnant.

Approximately twenty minutes seemed a fair duration of stasis for the first time. Longer periods might be endured but were sometimes fatal, not from local necrosis but from general intoxication. Immunization resulted from successive applications of stasis, so that the duration might finally be made as long as 2 hours, which could not be borne safely at the

first operation. It was remarkable that both the epithelium and the nerve ganglia of the pancreas could survive the lack of circulation for such periods. The completeness of the occlusion could be demonstrated by cutting some of the smaller vessels of the pancreas, which failed to bleed while the clamps were in place but bled freely so as to require ligature after their removal.

The ideal goal of experiments of this kind would be to produce diabetes with the entire pancreas in position, so as to imitate fully the condition in man. Granted the means of producing an adequate single injury or series of injuries, there is theoretically no reason why this goal should not be attained. The actual attempts to make dogs diabetic without removal of pancreatic tissue failed. It was impossible to injure the pancreas sufficiently by a single application of stasis. Repeated operations caused the formation of adhesions and scar tissue, which interfered with the application of clamps and finally caused death through the dissection or crushing made necessary. Obviously, the smaller the pancreas remnant and the closer the animal already is to diabetes, the more easily is diabetes produced by stasis. The limits of the method are fixed, however, not so much by the size of the pancreatic remnant as by the feasibility of repeated clamping of its vessels. This condition is practically fulfilled only in the uncinate process, which can be easily isolated with the exception of a stem of vessels at one end and vessels and duct at the other. Two clamps therefore cut off its circulation completely, and under favorable conditions the operation can be repeated almost indefinitely. The maximum size of remnant with which it has been possible to produce diabetes by this means is therefore about a third of the pancreas. This suffices to establish the general principle involved, especially in view of the possibility that the dog is naturally less susceptible to diabetes than man.

Experiments along this line were attempted with a more susceptible species, namely the cat, which becomes diabetic with removal of only $3/4$ to $4/5$ of the pancreas, but failure resulted because the operations were so badly borne from the standpoint of general health. Only some of the typical results with dogs, therefore, are summarized in the following protocols.

A. *Experiments without diabetes*

Dog E5-44.— The pancreatic circulation was clamped for one hour, and specimens then taken for microscopic examination. In this and similar experiments the appearance of very slight postmortem change was all that could be noticed.

Dog E5-83.— This was a puppy only a few weeks old, weighing 2.9 kgm. Aug. 31, 1917, the splenic process and body of the pancreas were removed, and stasis applied to the uncinate process for 1½ hours. The result was fever, prostration, and death in 24 hours. The pancreas remnant was swollen and tense, only slightly hemorrhagic, and without gross necroses. Microscopically, the dominant feature was the great outpouring of fibrinous exudate along all the connective tissue septa, with a sprinkling of leukocytes and occasional hemorrhages. These processes invaded the parenchyma only slightly, though leukocytes and some exudate were found in places between the acini, rarely involving the islands. Both acini and islands were somewhat blurred in their markings; the cells appeared slightly swollen and edematous; and the cytoplasm in the islands especially was pale but yet showed no resemblance to the true hydropic change. Neither necroses nor mitoses were found, though no adequate search for the latter was made in any of this work.

Dog E5-50.— Female; toy bull terrier; age 8 years; excellent nutrition; weight 10 kgm. May 24, 1917, removal of all but uncinate process of pancreas. June 15, stasis of remnant for 30 minutes. Death occurred from another operation June 28. The pancreas remnant was grossly swollen and inflamed, weighing 20.7 gm. in contrast to the original estimate of 8 gm. Microscopically, fibrosis and round-cell infiltration were the principal feature, chiefly between the lobules but also spreading diffusely between the acini. In some areas the connective tissue formation was dominant; the acini were in all stages of involution and degeneration, and islands were practically non-existent, as though they had been destroyed to even greater extent than the acini. In other areas the bands of invading connective tissue were slender, the acini seemed uninjured, and numerous normal appearing islands were present.

Dog E5-51.— Female; bull terrier; white; age 6 years; good condition; weight 18 kgm. May 24, 1917, removal of pancreatic tissue weighing 26 gm., leaving only the uncinate process estimated at about 13 gm. June 15, the circulation of the remnant was clamped for 55 minutes. Glycosuria followed the feeding of bread and soup on June 16, but was then absent even with addition of glucose.

June 27, operation showed a normal appearance of the pancreas remnant. A small specimen was removed, and stasis then applied for 75 minutes. The microscopic examination revealed nothing abnormal except trivial fibrous thickenings, a few small groups of round-cells, and irregularity in size and shape of the acini. Islands were present

in fair number and size; their form was often irregular, and a considerable proportion also seemed to lack a capsule. Such signs may indicate repair or regeneration after injury.

Stasis was again applied July 27 for 50 minutes, Aug. 3 for 1 hour, and Aug. 24 for 1½ hours, without diabetes. The dog lost weight down to 15 kgm. and after the last operation became increasingly ill. Sept. 7, the pancreas remnant was found involved in a large abscess of foamy, foul smelling pus, in which cultures demonstrated the gas bacillus and numerous other organisms. The dog survived but did not thrive. Operation on Sept. 28 disclosed an abscess of creamy pus between the duodenum and liver, in which smears showed apparently only streptococci. The dog died over-night. The pancreas was badly inflamed and sclerosed in gross, but there had been no diabetes. No microscopic specimens were taken in the later operations, and the tissue at autopsy was worthless because of postmortem change.

Dog E5-03.— Male; mongrel; black and white; age 5 years; good condition; weight 15.5 kgm. March 1, 1917, clamps were applied for 10 minutes to block circulation in entire pancreas and adjoining portion of duodenum, in order to avoid dissecting out vessels. March 23, this was repeated for 20 minutes, April 6 for 40 minutes, and April 19 for 30 minutes. Probably the portal vein was blocked in the last operation, for there was extreme shock, and after prostration and bloody diarrhea the dog was found dead April 21. Autopsy showed appearances of congestion and inflammation in both the pancreas and the bowel. Microscopically there was the usual swelling and infiltration of the pancreatic septa, but little change in the parenchyma. Islands in particular seemed to vary within normal limits. Cytological observations were impossible on account of postmortem change.

Dog E5-84.— Puppy aged about 3 months, in good condition, weighing 3.9 kgm. Sept. 7, 1917, removal of splenic process and most of body of pancreas weighing 21.1 gm., left a remnant estimated at 5.7 gm. Stasis of this remnant was then maintained for 55 minutes. Thereafter glycosuria was absent on bread and milk diet, and was only transitory with addition of 75 gm. glucose, which was all the pup would take. At a second operation on Sept. 28, the pancreas remnant appeared normal, and stasis was maintained for 85 minutes. The animal was weak and unwell thereafter, and was found dead on the morning of Oct. 4. The pancreas remnant appeared inflamed, and weighed 7 gm. Microscopically it was enormously infiltrated with leukocytes throughout the parenchyma, whether on account of infection or as a reaction to simple cellular injury was not determined. A large proportion of the acini seemed to be undergoing rapid degeneration or necrosis, and their remains were invaded by leukocytes. Few islands could be identified. One was found which was intact, and several others were recognizable amid leukocytes which were apparently destroying them. The only nerve ganglion seen was free from leukocytes and apparently uninjured.

Dog E5-48.— Male; bulldog mongrel; yellow; age 4 years; excellent

nutrition; weight 15.3 kgm. May 24, 1917, removal of splenic process and most of body of pancreas, weighing 29.7 gm., leaving uncinate process and portion of body about main duct, estimated at 15 gm.

June 15, the pancreatic circulation was clamped for 40 minutes. After removal of the clamps the tissue flushed bright pink, and in this condition a tiny specimen was removed for microscopic examination. This was nearly normal except for small interstitial hemorrhages, chiefly along the septa, sometimes between the acini, but never in the islands. The acini were crammed with homogenous staining zymogen, which crowded the basophilic substance into a narrow rim. Their nuclei seemed slightly pyknotic. The islands were not congested, but on the contrary their capillaries were contracted and bloodless. Their cells were not perceptibly changed.

Diabetes remained absent on bread diet with 100 gm. glucose. June 27, operation showed the pancreas remnant buried in omental adhesions but not greatly changed. A tiny specimen was removed, and then stasis applied for 75 minutes. The specimen showed no definite abnormalities.

The dog refused food, vomited, and was found dead of peritonitis on June 30. The pancreas remnant, appearing swollen and inflamed, weighed 23.4 gm. Microscopically both old and recent changes were seen. There was a definite organized fibrosis practically throughout the remnant, which had happened not to be represented in the small specimen of June 27. A more prominent feature was recent swelling and infiltration of the septa, with invasion of leukocytes also among the acini. Most of the acini were full of zymogen, but a minority were undergoing involution and degeneration. Islands were present in average number; they were never selectively damaged, but were sometimes involved in fibrous or leukocytic invasion from the adjoining acini. Postmortem changes prevented cytological observations. Two ganglia and several nerves encountered in the sections appeared normal.

Dog E5-41.—Female; mongrel; yellow and white; age 1 year; well nourished; weight 12.5 kgm. Nov. 30, 1917, removal of pancreatic tissue weighing 12.9 gm., consisting of the splenic process and most of the body, left the uncinate process and part of the body surrounding the main duct, estimated at about 10 gm.

Dec. 6, the pancreatic circulation was blocked for 35 minutes, Dec. 19 for 50 minutes, and Jan. 31 for 70 minutes. The dog continued to thrive, developed no diabetes, and died in an operation on March 9 at a weight of 15.2 kgm.

The pancreas remnant on Dec. 19 appeared normal or slightly atrophic in gross. Microscopically it showed inter- and intra-lobular fibrosis and round-cell infiltration, with widespread involution and degeneration of acini in some areas and nearly normal parenchyma in others. Islands were lacking only where the general destruction was greatest, and were abundant and apparently normal in the areas where the parenchyma was uninjured or regenerated.

On Jan. 31 the remnant was apparently of the original size but was

distinctly firmer than normal. Microscopically, the connective tissue formation seemed less marked than before. Normal appearing acini were mingled with groups and long strands of poorly differentiated cells, perhaps representing epithelial proliferation. Islands were noticeably large and numerous, but often irregular in form.

The pancreas remnant at autopsy weighed 13 gm. and appeared slightly shrunken and hard. Microscopically it was about as before, with fibrosis dominant in some areas and nearly normal parenchyma in others. Islands on the whole were scarce and small, but no selective fibrosis or active injury of them was discoverable.

B. Experiments with diabetes

Dog D4-93. — Male; fox terrier; yellow and white; rather old; medium nutrition; weight 8.5 kgm. Feb. 5, 1917, removal of pancreatic tissue weighing 13.1 gm. The remnant, estimated at 8 gm., consisted of the uncinate process and adjoining tissue about the main duct. Feb. 23, stasis was applied to the remnant for 20 minutes. The dog seemed to recover promptly and well, but the next day was prostrated and vomiting. Glycosuria was absent until a little meat was eaten on Feb. 25, when there was 0.43% sugar in 139 cc. urine. The next day a little bread was eaten, with the result of 2.4% sugar in 539 cc. urine. With improving appetite the glycosuria continued to increase, reaching values of over 5% in over a liter of urine. This glycosuria continued after change to protein-fat diet on March 9.

March 17, when the weight was 7.3 kgm., operation showed the pancreas remnant slightly hardened and shrunken toward the duodenum, but soft and normally lobulated toward its free extremity. Tissue weighing 0.42 gm. removed from this softer portion was almost normal in microscopic structure, with only occasional suggestions of fibrosis. Acini were normal and well filled with zymogen. Islands were slightly but perhaps not abnormally scarce, and medium in size. There was hydropic degeneration in a majority of the cells, but no fibrosis or other changes.

Dog E5-55. — Male; Dachshund mongrel; black and tan; age 6 years; slightly obese; weight 15.4 kgm. May 24, 1917, removal of splenic process and most of body of pancreas, weighing 30.3 gm., left the uncinate process and part of body about main duct, estimated at 20 gm. (about 2/5). The vessels to the remnant were clamped for 25 minutes. Glycosuria was absent on bread diet but heavy with addition of 100 to 150 gm. glucose daily beginning May 28. It tended gradually to diminish, so that on June 21 the glucose was increased to 200 gm. daily. Nevertheless the glycosuria finally stopped on June 27. In an operation on that date, the pancreas remnant appeared practically normal. Tissue weighing 0.1 gm. taken as a specimen showed only traces of fibrosis and normal conditions in acini and islands, except for doubtful vacuolation in the latter. Stasis of the pancreas remnant was maintained for 1 hour. The dog refused food and remained without glycosuria till death from a pancreatic abscess on July 11. The

remnant at autopsy was considerably inflamed but without extensive destruction of parenchyma. Cytological study was prevented by post-mortem change.

The continuance of heavy glycosuria for more than a month on glucose diets must be interpreted as a transitory diabetes. It is noteworthy that this occurred in the presence of 2/5 of the pancreas and an abundance of normal appearing islands.

Dog E6-60.—Male; Airedale mongrel; age 2 years; slightly thin; weight 13. kgm. June 12, 1917, most of the body of the pancreas was removed by careful blunt dissection so as to save the vessels and ducts. June 27, both uncinata and splenic processes seemed normal and free from atrophy. Tissue weighing 9.3 gm. was removed from the uncinata process, leaving a remnant estimated at 5 gm. This and the splenic process were then subjected to stasis for 30 minutes. Glycosuria remained absent.

July 20, the uncinata remnant was found apparently normal but the splenic process slightly hardened and shrunken. Both were subjected to stasis for 70 minutes. Glycosuria was transitory thereafter on bread diet with 100 gm. glucose.

Aug. 31, both pancreas remnants were found in apparently normal condition and free from adhesions. Stasis was maintained in both for 80 minutes. Glycosuria was absent on bread diet but continuous with addition of 100 gm. glucose. It continued heavy after glucose was stopped on Sept. 27, but ceased with change to meat diet on Oct. 10. It returned when bread feeding was resumed. With another change to meat diet on Oct. 23, glycosuria diminished but did not cease till Oct. 28. The dog meantime was failing rapidly and died in extreme emaciation on Oct. 31.

The uncinata remnant appeared little changed, but was not weighed. The splenic remnant had entirely disappeared amid the adhesions in this region, presumably because of some irreparable damage to the vessels or ducts or both. Microscopically there was variable fibrosis in the uncinata remnant. In some areas it was chiefly interlobular as usual. In many portions, however, there was almost a specific fibrosis and round cell invasion of the islands, while the acinar tissue was left relatively free. This was especially interesting because it was the only observed instance of such selective fibrosis of the islands. Where not fibrosed the islands were small and reduced in number. Slight vacuolation was present in their cells.

Dog E5-82.—Female puppy, aged 2 or 3 months, in good condition at a weight of 2.1 kgm. Aug. 3, 1917, removal of splenic process and body of pancreas, weighing 7.8 gm., left the uncinata process estimated at 3 gm. The vessels to the remnant were clamped for 75 minutes. Heavy glycosuria occurred within the first 24 hours, but was negative thereafter on bread diet with addition of from 25 to 150 gm. glucose.

Aug. 31, with the puppy thriving at a weight of 3.8 kgm. operation showed the remnant normal in gross appearance. Tissue weighing 0.1 gm. was removed as a specimen, and stasis was applied for 90

minutes. The specimen showed no abnormalities. The acini were normal in form and fullness, and islands were abundant and normal. Slight glycosuria ensued on bread and milk diet, and became heavy with addition of 25 gm. glucose on Sept. 3. It gradually declined, rose again with increase of glucose dosage to 75 gm. on Sept. 12, but ceased Sept. 18.

Sept. 28, at a weight of 4.75 kgm., operation showed the pancreas remnant normal in appearance and free from adhesions. Stasis was maintained for 1 $\frac{3}{4}$ hours, without removal of any tissue. Glycosuria was absent till milk was fed on Sept. 29, and thereafter was heavy on bread diet the following 3 days, and with another change to protein-fat required 3 days to clear up. Glycosuria was then kept absent on this diet, but the animal failed to thrive and died Nov. 11 at a weight of 2.6 kgm.

The pancreas remnant, normal in appearance and consistency, weighed 2.9 gm. Microscopically there was slight fibrosis, chiefly interlobular in distribution. The acini were irregular in form and fullness. Islands were almost absent in some slides, but present in fair numbers in others. None of those seen were directly invaded by fibrosis. There was also no vacuolation. One normal nerve ganglion was found.

SUMMARY AND CONCLUSIONS

1. Though spontaneous diabetes is evidently rare in dogs, pancreatitis seems to be more common. The incidence of eight cases in over a thousand animals, observed in this series, is less than 1 per cent., but could properly be compared only with a corresponding series of human individuals composed chiefly of the young and seemingly healthy. In the dog, as in man, pancreatitis seems to become more frequent with advancing years, and the most of these cases were found in senile and obese animals. The absence of diabetes, even when dogs with advanced pancreatic sclerosis were kept under observation for long periods, is readily explained by the type of pancreatitis, which in these animals was interlobular and accordingly spared the islands.

2. No specific influence of infection was observed. Infections involving the pancreas produced no more diabetic tendency than an equal degree of inflammatory damage from some other cause. Acute and chronic general infections, or localized abscesses carried for long periods in different parts of the body, never caused a perceptible diabetic tendency or fibrosis, hyalin degeneration, "atrophy" or other visible changes in the islands. No evidence was found that the islands are any more

susceptible to infectious or toxic injury than the acinar tissue. These negative findings carry no weight against the probability that infection or intoxication is responsible for diabetogenic lesions of the islands in man; for such lesions occur exceptionally rather than regularly, and neither diabetes nor permanent island changes are found in the great majority of human patients with infections.

3. The principal study of this paper consisted in the attempt to reproduce in dogs the most puzzling feature of the clinical pathology of diabetes, namely the occurrence of this disorder in the presence of large masses of healthy appearing pancreatic tissue. A clue was given by the evidences of old inflammatory damage found with few if any exceptions in the diabetic human pancreas, and by certain atypical results in partially depancreatized dogs. Though the diabetes in such animals ordinarily depends upon a strictly quantitative removal of pancreatic tissue, rare exceptions of the following types were encountered: (a) diabetes with a large pancreas remnant resulting from hypertrophy of an originally small remnant; (b) diabetes following fibrosis and atrophy of an original large remnant; (c) a large remnant which either maintains its size or hypertrophies markedly, so that diabetes occurs in the presence of a surprisingly large mass of healthy appearing parenchyma. Island tissue was usually scanty in such pancreas remnants, but the loss was evidently often due to hydropic degeneration, while some examples showed that diabetes might occur with numerous islands present. These accidental observations proved that the puzzling conditions of human diabetes could in some way be reproduced in dogs.

4. These observations formed a series which suggested that inflammation following the operation in these accidental cases gave rise to destructive and regenerative processes, ending in simple repair, atrophy or hypertrophy according as one or the other might predominate, while islands were either destroyed or functionally damaged so as to become susceptible to the hydropic degeneration resulting from overfeeding. In this connection it was uncertain whether the old islands were thus subject to some lasting but invisible impairment, or whether they were replaced by new-formed islands of inferior functional capacity. The principal experiments consisted in verifying this hypothesis by the intentional production of acute

pancreatitis in two ways, first by mechanical trauma of the pancreas remnant, and second by occlusion of its circulation for periods of 20 minutes to 2 hours. In this way the characteristic pathology of human diabetes and of the accidental cases in dogs was experimentally duplicated, and diabetes was produced with approximately one-third of the pancreas present. Exceptionally this remnant suffered extreme sclerosis, with consequent hopeless progress of the diabetes; generally the end result was only slight fibrosis, as in the great majority of human cases; but a few examples demonstrated that complete anatomic repair could ensue, leaving the diabetes as the only lasting effect of the acute inflammation.

5. Though the existence of chronic pancreatitis must be recognized (as from a chronic infection such as syphilis, from repeated or prolonged injuries such as the backing up of infected bile, or the simple stasis of the toxic pancreatic secretion itself by fibrosis following an acute injury), these experiments suggest that the use of this term should be restricted in a sense which carries three important practical applications.

First, the reproduction of the familiar pictures of more or less fibrosis in the pancreas by an acute inflammation indicates the possibility that the alterations in the human pancreas often represent not a chronic process but merely the vestiges of a former acute injury.

Second, the abnormalities in the diabetic pancreas are to be interpreted not merely in terms of the visible destruction of parenchyma, but rather as evidences of previous damage, the extent and importance of which in a diabetogenic sense can by no means be accurately measured by the existing remains.

Third, these consequences of acute inflammation are rarely progressive in dogs, and the resulting diabetes is subject to dietary control like that following simple partial pancreatectomy. Whatever acute injuries the islands sustain, their subsequent preservation or destruction depends upon the diet and the occurrence or non-occurrence of hydropic degeneration. The mere existence of fibrosis in the human pancreas therefore does not show a progressive pathologic process, and the possibility of prolonged successful dietetic control thus becomes explainable.

NOTES ON THE FIGURES

Fig. 1. — Characteristic pancreatic section of Dog B2-67. The islands are largely protected by their central position, and diabetes is therefore absent. Hydropic changes are likewise absent from the islands, notwithstanding the advanced pancreatic atrophy and the extreme general malnutrition.

Figures 2 and 3. — Diabetes with sclerotic pancreas remnants. Fig. 2 shows interacinar fibrosis breaking up an island. Most of the surrounding acini are fairly well preserved, and the island outline still remains, but the island cells would be difficult to recognize except for the characteristic hydropic change.

In *Fig. 3* the sclerosis is more advanced. The architecture of acini and islands is completely broken up. Island cells would be indistinguishable from the numerous involuted acinar cells or from duct cells, and it is doubtful if the special granule stains would give any clear differentiation in this kind of tissue. Nevertheless the wide vacuolation of the beta cells with severe diabetes is typical and unmistakable. Pancreatic atrophy therefore does not prevent this change.

Fig. 4. — Apparent new formation of islands in a pancreas remnant, without diabetes. A similar picture was published from an animal in the Harvard series¹⁰. The cross section of the supposedly new-formed islands in the dog is generally elongated or irregular. The so-called "morula" type of islands, which are interpreted as homologous structures in some human cases of diabetes (paper 7) are generally rounded in cross section. In this figure the island in the center of the right border, round in form and without capsule or the usual capillary and trabecular framework, is practically identical in appearance with the "morula" form in man.

Fig. 5. — Diabetes of traumatic origin (dog D4-14) and similar animals). The diffuse or interacinar form of fibrosis closely imitates that of many human cases. Acini and islands are irregular in form and size, as in many human cases, because of this scarring from a former acute inflammation. The diabetes is not due to simple lack of islands, which are abundant in number and size, so that a functional injury has evidently been produced as in human cases. The mixture of normal appearing and widely vacuolated island cells is plain even under low magnification.

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9. (7), pp. 387, 390.
10. (1), Fig. 8.

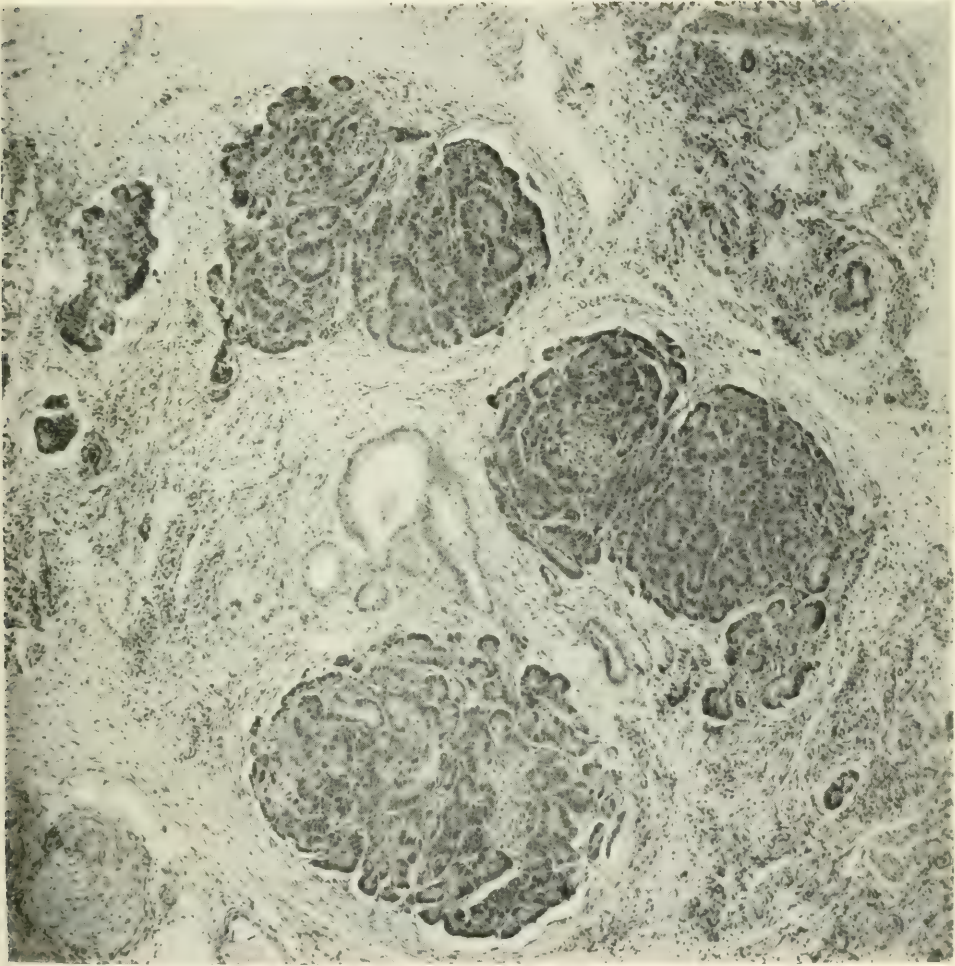


FIG. 1.

× 100.

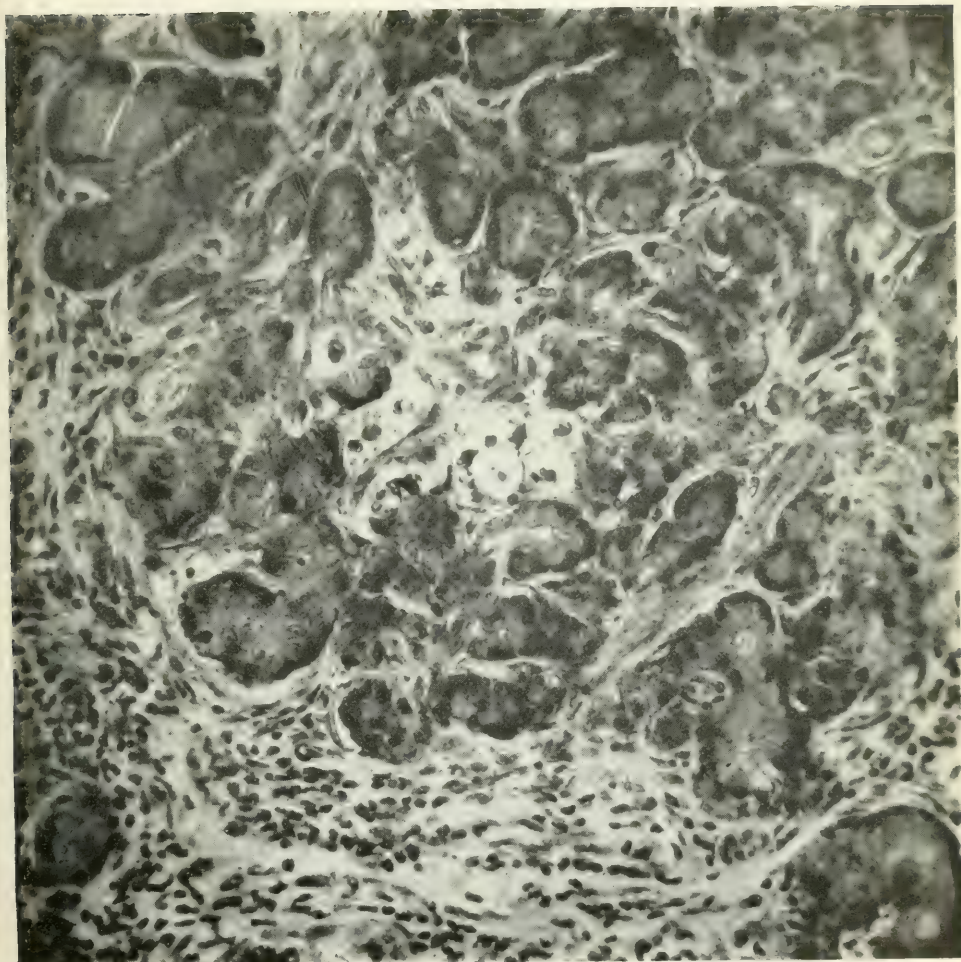


FIG. 2.

× 400.

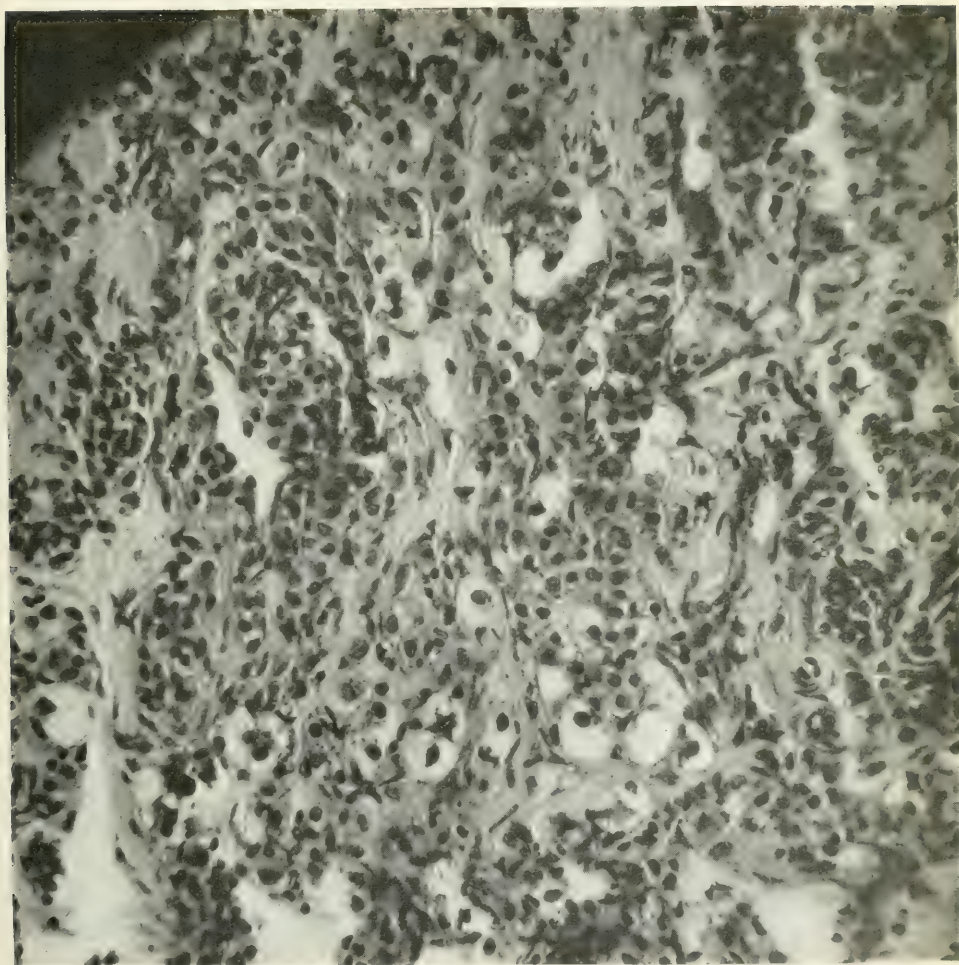


FIG. 3.

× 400.

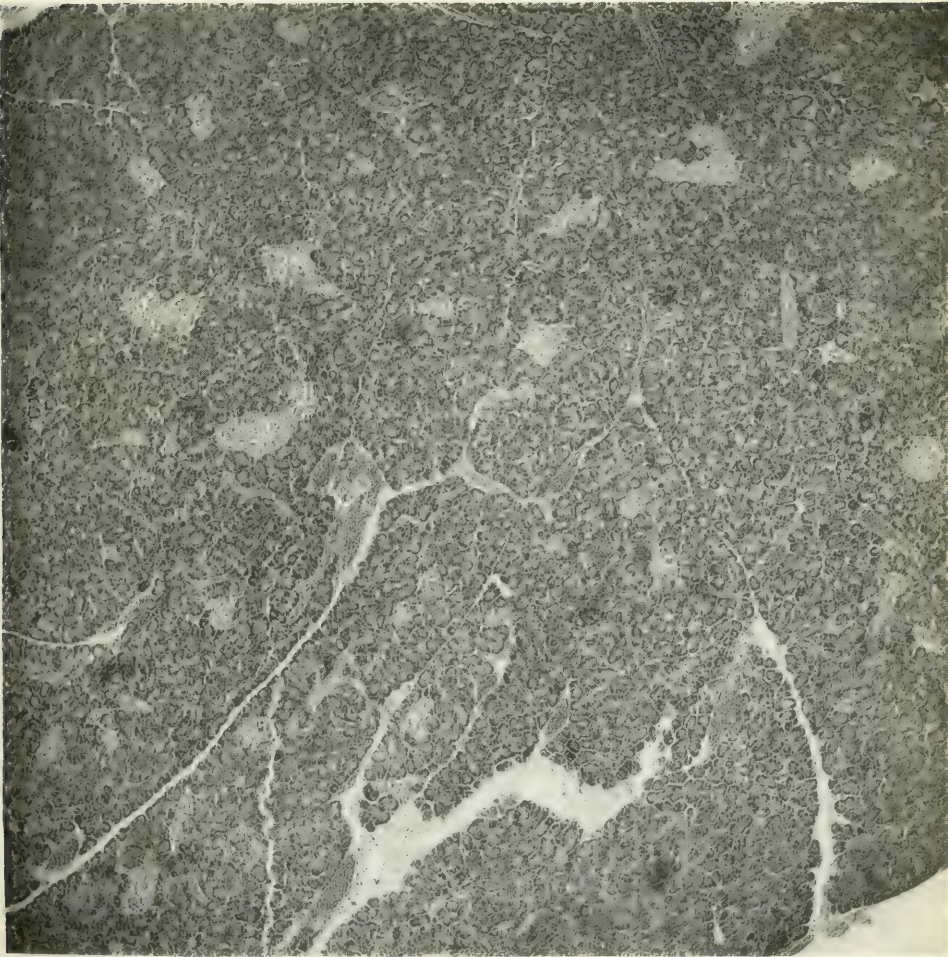


FIG. 4.

× 65.

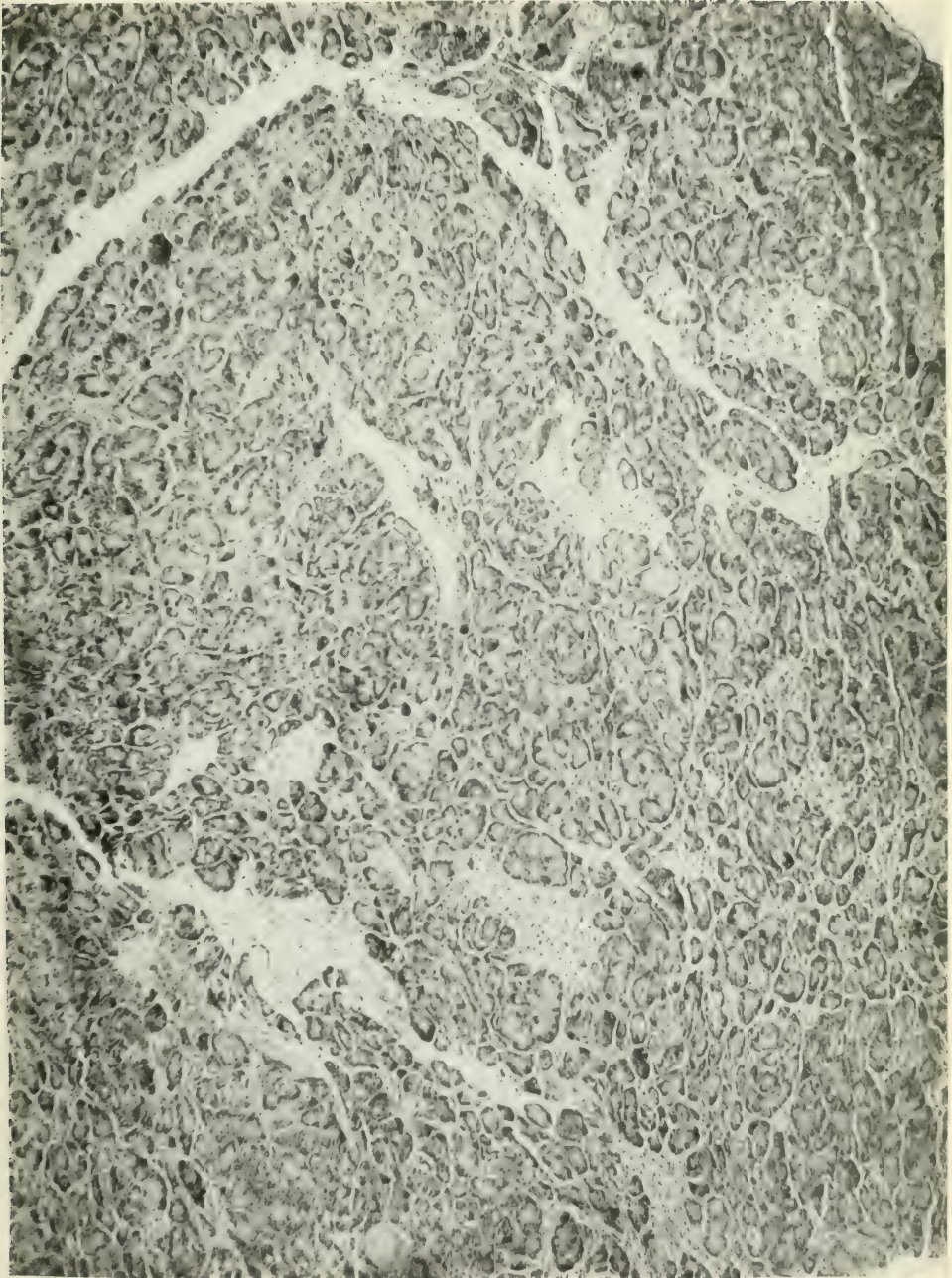


FIG. 5.

× 82.

EXPERIMENTAL STUDIES IN DIABETES

SERIES III. THE PATHOLOGY OF DIABETES.

7. MICROSCOPIC STUDIES OF THE PANCREAS IN CLINICAL DIABETES.

By FREDERICK M. ALLEN.

*From the Hospital of the Rockefeller Institute for Medical Research,
New York.*

Complete autopsies were performed upon several cases of severe diabetes treated in this hospital, and permission for removal of the pancreas alone was obtained in several others. As usual in cases of pure diabetes, nothing was found elsewhere in the body to throw any light upon the origin or nature of the disease. Also in these cases the pancreas appeared normal to gross examination in color, lobulation, consistency, size and weight. Subnormal size of the pancreas due to true developmental deficiency is doubtless a great rarity, and the occasional observations of this kind in diabetic cases are explainable as a rule by obvious atrophy and fibrosis or by the general wasting of organs with emaciation. The negative gross findings conform to the general experience of pathologists, and this report is confined to the microscopic examinations because it is believed that these alone afford any information concerning the etiology.

The first 7 cases belong to the series published in Monograph No. 11 of the Rockefeller Institute, and are recorded under the numbers which they bore in that Monograph, where also the details of the clinical history will be found. No detached study of diabetic pathology can be complete, for correlation with the clinical record is often necessary for interpretation of the findings. At the same time a microscopic diagnosis is possible in a high proportion of cases without regard to any clinical data, as illustrated in this and the following paper.

I. CASES FROM ROCKEFELLER INSTITUTE MONOGRAPH No. 11.

CASE No. 4.

Clinical Summary. — There was a marked hereditary history, including one case of cancer and several of nervous trouble; but in particular, a paternal great-uncle died at the age of 6 years of diabetes. The patient was one of two children, both apparently strong and well. The elder developed diabetes at the age of 2-1/2 years and died at 4 years. The present patient had bilateral cervical abscesses at 2 months, then several slight attacks of bronchitis in infancy, "rheumatism" in legs for 4 days at 4 years, measles at 5, chicken-pox at 6, and several attacks of tonsillitis subsequently. None of these troubles seemed serious, and the child seemed entirely healthy, but was forbidden candy for fear of diabetes. Polyuria and polyphagia were noticed at the age of 5 and diabetes immediately diagnosed. The best obtainable treatment was employed, but glycosuria was present most of the time and downward progress was slow but continuous. Acidosis gradually developed, and at 11 years albuminuria also began. He was admitted to the Rockefeller Institute Hospital at the age of 12, in an extreme stage of emaciation, acidosis, and blindness due to retinitis. The active symptoms were cleared up and kept under control during 4 months, but the occasional stealing of food necessitated exceptionally severe undernutrition, so that death occurred from inanition Oct. 19, 1914.

Pancreas. — There is some relative fibrosis through shrinkage of parenchyma, but also the impression is given that some thick septa and fibrous patches are abnormal, especially for a child. The acini are small but regular in form, ranging in zymogen content from half full to nearly empty; no involution; no fibrous invasion. Islands are widely variable in different slides, and are described by the following statements. (1) In general there is a marked scarcity, so that frequently island-like structures are nearly or completely absent from large sections. (2) Thorough search revealed no vacuolation of island cells. (3) A very few islands are present which appear entirely normal; so few that it is generally necessary to search 5 or 10 slides to find one of them. (4) Slightly more numerous are islands with more or less fibrosis, but with fully normal appearance of the remaining cells. (5) Some islands are nearly replaced by fibrous and hyalin formation, and the remaining cells are flattened and shrivelled (Fig. 13). (6) The great majority of islands, whether showing much fibrosis or almost none, are extremely "atrophic" in the sense of Weichselbaum; i.e., the cells are shrunken, consisting of pyknotic nuclei with a narrow markin of cytoplasm, and look almost like the round-cells that are often scattered among them. (7) Occasional slides contain numerous structures (Fig. 14) which might hastily be classified as normal islands, but which can only be called "pseudo-islands". The writer has had the opportunity of showing them to Bensley, Warthin and other experi-

enced observers, who are agreed that the structures are certainly not of island nature or origin. They are distinguished from islands by the lack of the characteristic capillary and trabecular structure and by the type of cells, which have a larger, denser nucleus and particularly a denser, more deeply staining cytoplasm. One suggestion has been that they are modified acinar tissue, because of the seeming existence of basophilic substance in the cytoplasm. A more plausible assumption is that they are abnormal proliferations of ducts. They are free from any fibrosis or "atrophy". W. B. Martin made several granule stains of this tissue, but no differentiation of cell types was obtainable and no decision was afforded concerning the nature of the doubtful structures.

Remarks.—1. Diabetes could be positively diagnosed microscopically in this case from the extreme scarcity of islands and the fibrosis and "atrophy" in those remaining.

2. The absence of hydropic degeneration corresponds to the absence of active symptoms. It is still probable that such degeneration during the years of active symptoms was one cause for the final scarcity of island tissue.

3. The supposition that the "atrophic" island cells are almost or entirely functionless would agree with the minimal tolerance, which here seemed actually too low to support life.

4. The nature of the "pseudo-islands" is unknown. They might be interpreted speculatively as representing an abortive attempt to form islands after the power of forming true islands has been exhausted, but more probably they are a consequence of pancreatitis.

5. The fibrosis of islands probably indicates some infectious or toxic injury through the blood stream, perhaps originating from one of the early childhood infections. In any event, the pathology in this hereditary case is entirely similar to that found in cases of diabetes in general.

CASE No. 8.

Clinical Summary.—The family history was negative. The patient was a printer, aged 29, healthy except for measles, mumps, and chicken-pox in childhood, occasional colds, and a slight pleurisy 4 years previously, which kept him in bed only one day. His habits had been regular. He had been married one year, but his wife was never pregnant. Diabetes apparently began during his honeymoon, and was so severe that symptoms were never controlled, and the patient was finally received in a state of emaciation and pre-coma. In the hospital, glycosuria and acidosis were abolished by fasting and low diet as usual, but during 6 months they kept recurring in a fashion indicating some unusual difficulty. This at length revealed itself as pulmonary tuberculosis, which possibly had lain concealed from the time of the pleurisy 4 years before. Higher diets then permitted symptoms to return during about 2 months. To avoid coma, close restrictions were next resumed, so as to keep glycosuria almost continuously absent for a month.

Thereafter glycosuria was present for 11 days preceding death, which was chiefly from weakness, consciousness being retained up to the last few minutes.

Pancreas.—A minority of acini contain a little zymogen. The others are not only empty but often involuted, as frequently noticed in cachexia. Islands are present in fair number and size, without vacuolation, and with only slight fibrosis in a minority of them; but all show advanced "atrophy" (Fig 12). No distinct fibrous or inflammatory changes are found outside the islands.

Remarks.—1. No positive microscopic diagnosis of diabetes was possible in this case, though it was of the severest type. Diabetes could have been strongly suspected from the marked "atrophy" of islands, but the accompanying shrinkage and involution of the acinar tissue created uncertainty.

2. There are two explanations for the absence of hydropic degeneration. (a) Glycosuria had been absent up to the 11 days preceding death, and even then was somewhat mitigated by diet. This duration and degree of overstimulation is inadequate for marked vacuolation of island cells. (b) The shrivelled, "atrophic" island cells are probably incapable of hydropic degeneration.

3. The supposition that the "atrophic" cells are nearly or entirely functionless would agree with the lack of tolerance in this case, and also with the failure of such cells to show vacuolation on functional over-stimulation.

4. The involution of the acinar tissue is familiar in cachetic states and is not peculiar to diabetes. The reason why "pseudo-islands" occur in some diabetic cases and were absent in this and most other cases is unknown.

5. This pancreas is of the type that has sometimes passed as "normal" in diabetic autopsies. The diabetes presumably took its origin in whatever caused the "atrophic" change in the islands, whether this may have been an acute infection or a chronic intoxication. The case furnishes a good illustration of a specific island injury with no demonstrable damage of the acinar tissue.

CASE NO. 13.

Clinical Summary.—The patient was a girl of 11 years, with negative family history. She had always been the strongest of a family of 6 children, and constantly well except for whooping cough and measles before 5, mumps at 6, and adenoids which were removed at 6 years. Glycosuria began in April 1914, and the patient was received in the stage of moderate acidosis the following November. Almost continuous freedom from symptoms was then maintained until death from inanition on Oct. 16, 1917.

Pancreas.—The general structure is normal except for a few small patches of interacinar fibrosis. The form and arrangement of acini and lobules also seem irregular, suggesting a possible previous disarrange-

ment by inflammation. The zymogen content varies from half full in some sections to nearly empty in others, but there is no general involution or lack of acinar formation. Especially, the nerves and a few ganglion cells encountered in this pancreas appear normal, and in one slide three normal Pacinian corpuscles * are found.

Observations concerning islands are as follows. (1) A few slides contain some island-like areas which are obviously composed of involuted acini. (2) Occasional doubtful structures of the kind called "pseudo-islands" are also seen. (3) A very few normal appearing islands can be found. (4) The great majority of islands are markedly "atrophic" even when the surrounding acini seem healthy and fairly well filled. (5) The majority of islands show fibrosis varying from slight to marked. (6) The general scarcity of islands is noticeable but not extreme. (7) No vacuolation of island cells is found.

Remarks.—1. Diabetes could be diagnosed microscopically with strong probability from the scarcity of islands, and from the widespread fibrosis and "atrophy".

2. The absence of hydropic degeneration corresponds to the absence of active diabetic symptoms.

3. The association of minimal assimilative power with "atrophic" islands again points to a lack of function in these.

4. "Pseudo-islands" are again present, and may have some diagnostic import.

5. The fibrosis almost specifically confined to the islands is again suggestive concerning the origin of the diabetes.

CASE No. 15.

Clinical Summary.—Little was known of the patient, except that he was a book-keeper 42 years of age, had had diabetes for at least 2 years, but enjoyed fair subjective health until he suddenly went into coma. He was received in full coma and died within 2-1/2 hours, and less than an hour after an intravenous injection of 1 liter of 4% sodium bicarbonate solution.

Pancreas.—There is interacinar fibrosis throughout all sections, varying in degree from slight to moderate. There is an occasional sprinkling of fat cells. Only a few acini are seen suffering involution or destruction from strangulation, but many are distorted. The acinar cells are mostly about half full of zymogen. Islands are abundant in some sections, and in general are not noticeably reduced in either number or size. Nearly all show slight fibrosis and some degree of "atrophy". The latter is generally not extreme, but occurs as a sprinkling of few or many shrivelled and pyknotic cells among apparently normal cells. A slight round-cell infiltration generally accompanies. There is congestion of most of the islands, without hemorrhages. Only occasional slides show hydropic degeneration, and these only in a

* It may be noted that the function of these structures, which are numerous and prominent in the pancreas of the cat especially, is entirely unknown.

minority of islands. In some such islands only a few cells are swollen and vacuolated, while the others appear normal; in others nearly all cells appear as distended clear vesicles. In addition, there are rare island-like areas, occupied by a dilated capillary network and a few sprawling, widely separated columns of cells which resemble island or duct cells and are not vacuolated.

Remarks.—1. The relative richness of islands containing a considerable proportion of normal-appearing cells is evidence that this case was by no means as severe as the others, that death merely resulted from an easily preventable acidosis, and that a considerable food tolerance might have been attained under proper treatment.

2. The atypical island-like formations are probably proliferations from ducts which possibly have grown into the framework of destroyed islands. The diagnostic significance of these structures is unproved. If it is correct that they are a product of pancreatitis, their presence should for this reason raise the question of possible diabetes.

CASE No. 39.

Clinical Summary.—The patient was a school teacher, age 27. There was a strong neurotic element in the family, and one or possibly 2 cases of diabetes. The childhood diseases had included scarlet fever, said to have been followed by ear trouble and nephritis. The patient was very nervous but otherwise strong and well. She had been treated for diabetes since 1910, but had repeatedly brought back symptoms by departures from diet. She was admitted to the hospital in April 1915, and was kept symptom-free except for occasional violations of diet for the next 2 years. From April to June 1917, glycosuria was present on improper diet. On June 18 she was readmitted to the hospital with most intense symptoms, including acidosis which resisted treatment and caused coma death on June 20.

Pancreas.—The pancreas contains a sprinkling of fat cells singly and in groups, but no general fibrosis. Congestion and even hemorrhage are seen in places, but are possibly due to trauma in removal. The acini are regular, free from involution, and in zymogen content range from half full to nearly empty. Islands are numerous and large, often strikingly so. None are normal, and the abnormalities are remarkable in number and variety. A minority show slight fibrosis. The architecture of the majority is normal, but atypical forms are numerous. Some are strikingly large, sometimes elongated or irregular in shape, and occasionally connected by duct-like bridges, the whole suggesting a rank hyperplasia of island tissue. Some smaller islands belong to what the writer has called the "morula" type; i.e., they are almost solid masses of island cells without visible capsule to demarcate them from the acinar tissue, and without the characteristic capillary and trabecular framework, the visible blood supply ordinarily being no more than one small vessel. The majority of islands in this pancreas show hydropic degeneration (Figs. 5, 6, 7). Often 1 or 2 cells are more or less widely vacuolated while the others appear normal. Other

islands exhibit progressive degrees of involvement up to maximal exhaustion of all cells, as illustrated. A large minority of islands show "atrophy", which can also be traced through apparent stages. Sometimes only a few cells are thus dark and shrivelled. A liberal sprinkling of these is generally seen throughout the large, supposedly hyperplastic islands. Elsewhere occasional islands exhibit advanced "atrophy" of all cells. Sometimes vacuolated and "atrophic" cells are found in the same islands (Fig. 11). There is considerable tendency to grouping of the various changes, so that neighboring islands are often similar, but there are no uniform distinctions between the head, body and tail of the gland except a progressive increase of hydropic changes from head to tail. Marked differences exist between different blocks and different sections from the same block, but the different types of islands sometimes occur also in the same sections.

Remarks. — 1. The microscopic diagnosis of diabetes could not have been missed in this case, though the pancreas is of the kind which on routine examination after a late autopsy might have been passed as "practically normal".

2. The so-called morula islands are presumably new formations from ducts. In human tissues these are generally rounded in cross section, but in animals they are more often elongated. Their presence is suggestive of diabetes or at least of some pancreatic injury which has called forth strong regenerative efforts. The cells are of true island type and evidently functional, because they are strongly subject to hydropic degeneration, but there may be a question whether they are equal in functional capacity to the original island cells.

3. The customary presence of round-cells or more or less fibrosis in islands undergoing "atrophy" strengthens the supposition that this change is due to some infectious or toxic injury.

4. Diabetes evidently existed in this patient with an abundance of normal appearing islands present, and even the extreme stage of intensity was reached without any corresponding degree of island loss. While a functional deficiency is thus indicated, nevertheless, as usual in cases with islands thus present, the food tolerance was decidedly higher than in other cases of the series in which islands were absent or "atrophic". The functional overstrain of the islands by excessive diet was carried to the point of producing widespread hydropic changes in the islands which were otherwise normal in appearance. Animals which reach this advanced stage of hydropic changes can no longer be saved by treatment, and a clear reason is shown for the failure of treatment in this case.

CASE No. 71.

Clinical Summary. — The patient was a nine year old boy, with negative family history and with no infection or illness in his whole life as far as his parents (who were cultured people in very good social position) were aware. Diabetes began at the age of 7. Treatment at first was efficient. Subsequently diet was broken; the boy was admitted to

the hospital in coma, and died on the ninth day thereafter. The first 7 days of this period represented continuous fasting, which effected a slight clearing of the acidosis. Failure of strength then necessitated feeding, and death occurred from weakness and coma. The sugar excretion during the last 8 days was small (0.92 to 7.26 gm. daily), but the plasma sugar was constantly high (0.26 to 0.56 per cent).

Pancreas.—A slight increase of fibrous tissue seems suggested in places, but may be entirely relative, due to shrinkage. There is a light sprinkling of fat cells. The acini are generally small and the average zymogen content low, but there is no involution or loss of acinar arrangement. The island content varies according to the parts of the gland. In the tail the scarcity of islands is extraordinary; a dozen sections may be searched without finding one. The few that are found show extreme "atrophy". The number of islands found in the body and head is greater but still subnormal. Fibrosis is present in the majority, but never amounts to more than a slight thickening along the capillaries. Normal island cells are practically absent. The majority of islands are in the same advanced stage of "atrophy" as in the tail. Elsewhere groups of large or hyperplastic islands are seen with no atrophy, but with the most extreme vacuolation of every cell (Fig. 12). One small intra-pancreatic ganglion is encountered; the nerve cells and fibers appear normal as usual.

Remarks.—1. The deficit of islands is more than sufficient to afford a diagnosis and to account for the diabetes on a strictly quantitative basis; but there is no certainty that the diabetes may not have begun with a greater abundance of islands, the subsequent loss of which may have been due to hydropic degeneration.

2. The presence of fibrosis and "atrophy" in the islands, and perhaps also their small number, may be interpreted as pointing to an infectious or toxic injury as the original cause of the diabetes even in a child with no clinical history of illness. An acute pancreatitis may cause little immediate disturbance of health and may leave behind only a trivial fibrosis which gives no adequate idea of the extent of the original inflammation but is important as evidence that the organ was once the seat of such a disturbance.

3. One point which has been remarked upon by nearly all persons who have seen the hydropic changes is that these are seldom as intense and widespread in human patients as in diabetic animals. Occasional cases like the present one show that when human diabetes is sufficiently intense the vacuolation of islands may be fully equal to that in animals. The one difference is that unchecked diabetes in experimental animals generally runs a course measured in weeks or months, while the progress of human cases is generally slower. The island changes necessarily correspond. Though this pancreas was obtained within half an hour after death, the outlines of exhausted island cells are by no means as distinct or the general picture as sharp as in animal organs which are taken while the heart is still beating.

4. The microscopic findings readily account for the failure of treatment. They also show the hopelessness of attempting to save such a

patient by superficial devices such as administration of sugar, neutralization of acids by alkali, or removal of supposed toxic substances by any means whatever. Even if the patient had been received a week or two earlier, before the island exhaustion and associated metabolic failure had reached their extreme point, it is certain from the pancreatic findings that the food tolerance must have been minimal and probably insufficient to support life.

CASE No. 73.

Clinical Summary.—The patient was a girl of 3 years, with negative family history except for glycosuria in a grandfather. She herself had been entirely healthy and had never had an infection or illness as far as known to the parents, who were highly intelligent. Diabetes began at 2 years. Prompt treatment abolished glycosuria, but after 10 months of high-calory diets it began to return. Dec. 18, 1916, the patient was admitted to the hospital in an emaciated condition. Symptoms were then kept absent by rigorous undernutrition, but the severity of the case was too great to permit a living diet, and death from weakness occurred at home in July 1918, even though the diet had been increased to the extent of permitting a slight glycosuria for a brief period preceding. The family physician performed a prompt autopsy and forwarded specimens of the pancreas preserved in Zenker solution.

Pancreas.—Particularly in the tail the acini are regular, normal, and well filled with zymogen. There is a suspicion of unduly thick fibrous trabeculae in places and an abnormal number of fibroblasts, but nothing positive. Islands are fully normal in number in the tail and body. Slight fibrosis is present only in a minority, but all show "atrophy" in a moderately advanced though not extreme stage. Only one island is found in which a few cells seem to be partially vacuolated. In passing toward the head, small patches of fibrosis and round-cell infiltration in the parenchyma become evident; the islands are fewer and more of them are slightly fibrosed. All these islands likewise show moderately advanced "atrophy". A few "pseudo-islands" are seen.

Remarks.—1. The functionless character of "atrophic" island cells is indicated by the minimal food tolerance with large numbers of such islands in this and other cases, and by the fact that they are not subject to hydropic degeneration.

2. The evidence of this and other cases is that "atrophic" islands may persist for years or perhaps indefinitely without disappearing. This would indicate that the functionally useless cells are at least able to maintain their own existence. It may be noted incidentally that highly fibrous or hyalin islands likewise apparently survive for long periods.

3. The "atrophic" change apparently does not improve with time and is not benefited by the strictest diet treatment. A question is possible whether it may advance with time and be responsible for downward progress clinically. The practically stationary assimilative power

of this and similar patients, apart from the consequences of slight excesses of diet, proves that such an advance either does not occur or else is very slow.

4. Stress may again be placed upon the very slight fibrosis of a small number of islands, which may be the only indication of a past inflammation in some cases. With careful search of a sufficient number of sections, these small changes will seldom if ever be found wanting in a diabetic pancreas. The hypothesis of an infectious or toxic origin of the diabetes might, however, still be tenable in cases free from demonstrable lesions, under at least two conditions; (a) an acute inflammation may damage the pancreas so as to produce diabetes and yet the repair be so complete that no fibrosis remains, as demonstrated in a few animal experiments; (b) fibrosis is sometimes limited to a slight thickening of the capillary and trabecular framework of some islands, as in the present case, and if these islands are then lost by hydropic degeneration, it is conceivable that the fibrosis will no longer be demonstrable.

II. ADDITIONAL ILLUSTRATIVE CASES.

No. 1.

Clinical Summary.—The patient was a man about fifty years of age, who had untreated diabetes of long standing and died in the War Demonstration Hospital of the Rockefeller Institute from a large carbuncle of the neck.

Pancreas.—There are no special differences between different portions of the gland. There is slight diffuse fibrosis of the acinar tissue, in the form of irregularly spreading bands and small patches. In some slides there is also a moderate sprinkling of fat cells. The acini are irregular in size and fullness but essentially normal and uninjured by the fibrosis. Islands are noticeably numerous and large. A few appear normal in all respects. A few of "morula" form are present. The great majority show varying grades of fibrous and hyalin transformation, and in a large proportion the hyalin deposit is far advanced. Hydropic changes are also widespread, both in the hyalin islands and in some of those otherwise normal. (Figs. 9 and 10). Nearly all degrees of the process are seen in different islands, from those without vacuolation or with only a few vacuolated cells to those having the majority of their cells vacuolated. There is no "atrophy" of entire islands, but some cells especially in the fibrous islands are shrivelled in the characteristic manner.

Remarks.—1. The pathology is like that of some of the cases upon which the insular hypothesis was founded in the classical work of Opie; namely, an almost selective alteration in the islands with relatively little damage to the acinar tissue. The fibrous and hyalin alteration in question is generally recognized as due to some infection or intoxication, which in this case may be regarded as the cause of the diabetes.

2. The hyalin and hydropic changes are independent and frequently occur side by side.

3. The permanent loss of tolerance following an acute exacerbation of diabetes accompanying an acute infection is well explained by the widespread hydropic changes here present.

4. The case was one of inherently mild diabetes, which had existed many years without treatment, without preventing the patient from carrying on his regular work as a day laborer, but which was suddenly fanned into intensity by sepsis. With due allowance for the anatomic destruction in the islands, so many cells remained uninvolved that the basis of the diabetes must probably be sought partly in a functional change. Nevertheless it is practically certain from the microscopic findings that if the patient could have avoided the infectious complication he could by proper treatment have acquired a considerable food tolerance.

No. 2.

Clinical Summary.— On account of certain special features this case will be reported elsewhere in detail if opportunity affords. The family were intelligent poor people in a small New York town. Both parents were well, and there was no known case of diabetes in any of the ancestors or relatives. The patient was a boy of 11 years, the youngest of 7 children, of whom 3 had died of childhood diabetes, 1 of meningitis, and 2 were well at adult ages. The patient had always been moderately obese in a strong burly fashion, and had lived a healthful rural life without nervous or dietary excesses. He had pneumonia at 6 years, measles and mumps before that, and numerous attacks of tonsillitis at all ages. He had been troubled somewhat with urinary incontinence by day as well as by night, but otherwise was very sturdy and well. He distinctly remembered a day about 6 weeks before admission when, toward evening, he felt some peculiar sensation in his abdomen which he described vaguely as a dull pain or weakness. This recurred for 2 or 3 days in succession. It then disappeared, but immediately polyuria aroused the mother's suspicion and she sent him to the family physician, who found heavy glycosuria. This did not yield to a classical carbohydrate-poor diet, but the patient continued to be entirely well subjectively except for progressive loss of weight. He was admitted to the Rockefeller Institute Hospital Sept. 18, 1917, looking and behaving like a strong well boy, with physical examination entirely negative. Glycosuria was controlled by 6 days of fasting, and further undernutrition reduced the plasma sugar to normal. A diet of 50 gm. protein, 5 gm. carbohydrate and 950 calories then brought back hyperglycemia. Thereafter the diet was never above 600 calories and often as low as 100 calories, but hyperglycemia was continuous and traces of glycosuria increasingly frequent. After Dec. 14, sugar was excreted in quantitative amounts daily (always less than 15 gm.), together with increasing amounts of acetone. After Dec. 26 the daily sugar output averaged above 25 gm., and coma was imminent. Dec. 29, as coma was beginning in spite of alkali and all other measures, tonsillectomy

was hazarded on the desperate chance of finding some buried infection as the cause of the downward progress. A skillful 2-minute operation removed the tonsils without pain or disturbance of the patient, but no pus was found and the coma progressed uninterruptedly to death on Jan. 1. The general autopsy was negative as usual.

Pancreas. — Only slight fibrosis of the acinar tissue is found by careful search in a few of the slides. A light sprinkling of fat cells is more general. There are no consistent differences between different divisions of pancreas, but sharp differences exist between different blocks or sections and even between different areas of the same section. In some areas the acini are empty and contracted, but not involuted or degenerating; in other areas they are fully normal and about half full of zymogen. Islands are decidedly scarce, but those present are free from fibrosis. In the areas in which the acini are empty, all the island cells show shrunken cytoplasm and pyknotic nuclei in the manner of typical "atrophy", and are entirely free from vacuolation. In the areas where the acini contain zymogen, the islands are free from the appearance of "atrophy"; a minority appear entirely normal, but the majority show vacuolation, generally limited to a few cells. The nerves and ganglia encountered seem normal. Glycogen stains with Best's carmine were made from portions of the tissue fixed in alcohol. Occasional leukocytes found in the blood vessels were crammed with red granules, but the vacuolated island cells were free from glycogen, as in animals.

Remarks. — 1. A diagnosis of diabetes was possible from the scarcity of islands and the vacuolation.

2. The progressive changes which were looked for to explain what was regarded as the spontaneous downward progress of this case were not found, and the result remained a puzzle. Up to that time the writer had never seen a case of this character, but subsequent experience has shown that examples of even greater severity and progressiveness may be encountered in children, and that the outcome in the above instance is explainable by inadequate treatment. When the plasma sugar was reduced to normal, it was again quickly raised above 0.2 and even above 0.3 per cent by a diet of over 900 calories. The subsequent diets were low, but not low enough to reduce this hyperglycemia. In some exceptional cases more recently it has been necessary to undernourish a fairly well-looking child to a state of weakness and emaciation before the plasma sugar could be kept normal, but even in these cases of extreme severity life has at least been maintained by this means and the downward progress apparently halted. In the present case the symptoms were partially controlled and the vacuolation of islands was accordingly moderate, but the fact remains that island cells were being lost by hydropic degeneration and no other form of island destruction was demonstrable.

3. Islands do not necessarily appear "atrophic" because the surrounding acini are empty, and it is not known whether the supposed "atrophy" in this case was genuine, or whether the terminal cachexia was responsible for a non-specific unhealthy appearance of both islands

and acini in certain areas. With allowance for this possible "atrophy" and for the general scarcity of islands, the anatomic findings still do not suffice to explain the unusual severity of this case. Furthermore, there is strong probability that a considerable number of islands were lost by hydropic degeneration, and that diabetes accordingly began with a greater abundance of islands present. A very marked functional deficiency of the healthy looking island cells must therefore be assumed.

4. The history was replete with infections, such as mumps, pneumonia and tonsillitis, which might have damaged the pancreas, and the slight but distinct fibrosis in some parts furnished evidence that pancreatitis had actually occurred at some time. The peculiar sensation which the patient experienced deep in the upper abdomen may possibly have indicated the first attack which initiated the diabetes or a recurrent attack which aggravated an existing undiagnosed diabetes. The remarkable family history may have represented a genuine consanguineal development of the disorder without a diabetic heredity, or unknown cases may have occurred in the ancestry. It must be assumed either that an acute pancreatitis, of severity out of all proportion to the trivial fibrosis left behind, destroyed some islands and seriously injured the function of the others so as to cause diabetes in a previously normal boy, or else there was an innate deficiency of the islands or their function so that diabetes resulted from a slight disturbance which would have been harmless in a normal person.

No. 3.

Clinical Summary.—A case of typical bronzed diabetes on the writer's service at the Rockefeller Institute Hospital was reported by Rous and Oliver,¹ who established the diagnosis by finding iron-containing pigment in the urine. The patient was at first kept free from glycosuria by regulated diet, with doubtful benefit because of the inevitable advance of cachexia independent of the diabetes. In the closing weeks of life moderate glycosuria was permitted. Death occurred with emaciation, ascites and jaundice such as are found with other forms of cirrhosis of the liver.

Pancreas.—The pancreas was approximately normal in size, distinctly brown colored, and hardened in consistency, so that it grated on cutting. Microscopically there is marked fibrosis, chiefly in the form of dense bands, both interlobular and irregular in arrangement, with slight to heavy pigment deposits in them at various places. The state of the acini ranges through all extremes, from zymogen fullness to complete involution, but the majority contain moderate quantities of zymogen and stain normally. The pigmentation of the acinar epithelium varies in different areas, but is widespread and in places remarkably heavy. Many acinar cells are crammed as full with pigment as they can hold. Other cells in the same acinus and other acini in the same lobule often contain very little pigment, and the reason for the selective distribution is not apparent. No pigment is visible in

the acinar lumina or in the ducts, so that excretion through the pancreatic juice is not thus demonstrable. Islands are scarce, as though many had been destroyed, and those remaining are often invaded by the fibrosis. Pigment deposits are the rule in them, but not as heavy as in the acinar tissue. "Atrophy" was not seen and an appearance of slight vacuolation was found in only one island.

Remarks.—1. The diabetes as usual rested upon the anatomic basis of pancreatic lesions involving injury and destruction of islands.

2. Hydropic changes may occur in the pigmented islands of bronzed diabetes the same as in other forms of diabetes. Here the vacuolation was slight because only slight symptoms had been permitted by the diet. The writer has seen specimens from one other case of hemochromatosis in which the vacuolation was marked.

No. 4.

Clinical Summary.—The patient was a man aged 55 years, who was admitted to the Presbyterian Hospital, New York, as an emergency case, underwent immediate operation, and died an hour afterward. The writer received specimens of the pancreas as part of a miscellaneous series, under the impression that they were non-diabetic. The finding of distinct hydropic changes seemed at first to be evidence that this vacuolation of island cells is not specific to diabetes. Inquiry then elicited the fact that the operation was for carbuncle, and a single urine specimen obtained had contained sugar.

Pancreas.—There was slight interacinar fibrosis in some places, with no sign of destruction of either acini or islands. The islands as a whole appeared fully normal in number, size and cytology. Occasional islands contained 1 to 3 or 4 cells which were markedly and unmistakably swollen and vacuolated.

Remarks.—1. These changes are so important and so commonly overlooked that Figures 2 to 4 are devoted to illustrating the appearances in this and two similar cases. If the tissue had not been unusually fresh and well preserved, the vacuolation might not have been demonstrable, and the pancreas might have been pronounced "practically normal".

2. Such cases are particularly important as examples of accidental death in the condition of early or mild diabetes, before extensive losses of island tissue by hydropic degeneration have occurred. It is evident that in some such cases, at least, diabetes may begin with an abundance of normal appearing islands present. As vacuolation is invariably a sign of overtaxed island function, it follows that a functional deficiency must be assumed in the cells which appear normal.

No. 5.

Clinical Summary.—No individual case can be reported, as none has occurred in the writer's series, but specimens belonging to the collections of other persons have been seen. This type of case, as far

as known, is always a mild diabetes in a middle-aged or elderly patient, and the course generally extends over many years.

Pancreas.—The particular characteristic, which requires mention for the sake of completeness, is the replacement of the pancreatic tissue to greater or less extent by adipose tissue. The slighter degrees of fatty infiltration are numerous, but in rare cases the pancreas may appear to be almost completely changed to fat, with ducts and more or less acinar or island tissue distributed through it.

Remarks.—1. As mentioned elsewhere, adipose invasion is generally on a par with fibrosis, and the parenchyma is probably thus replaced in consequence of injury from infection, intoxication, impaired blood supply (arteriosclerosis), or occlusion of ducts. The fatty change is said to be the end result after duct occlusion in the guinea-pig or rabbit, but in the dog and man sclerosis is far more common. The exact reason for the different results is not clear.

2. The occurrence or non-occurrence of diabetes depends as usual upon the degree of island injury. Scott² described an example of fatty atrophic pancreas resulting from stoppage of the duct by a tumor of the head of the gland. Here the islands persisted while the acinar tissue disappeared, and diabetes was accordingly absent. Any remaining areas of acinar tissue may appear normal or may be involuted, so that confusion of the small rounded cells with island tissue must be avoided.

No. 6.

Clinical Summary.—This may be made a composite case, to represent 3 in the present series in which a mild diabetes was merely an incidental diagnosis, and death occurred respectively from old age, pneumonia, and cardiorenal disease.

Pancreas.—There is a slight diffuse or patchy fibrosis, but no evident destruction of either acini or islands. The number of islands is either normal or only slightly reduced, and their cells show no specific alterations.

Remarks.—1. Even if there be a reduction of the number of islands below normal, it seems to be no greater than that found in some cases of so-called chronic pancreatitis without diabetes. The principal basis of the diabetes must therefore apparently be sought in a functional change. A high food tolerance is to be expected in such patients under treatment.

2. The absence of hydropic changes and the theoretical relations are discussed under case No. 8.

No. 7.

Clinical Summary.—A man of 59 years was admitted to the Rockefeller Institute Hospital on April 11, 1913, with the diagnosis of lobar pneumonia, suppurative pleurisy, and diabetes mellitus, and was dis-

charged after recovery from his infection on May 1. He was readmitted Dec. 18, 1915, with another attack of lobar pneumonia, and died Dec. 25. A trace of sugar was reported in the urine of Dec. 19. Otherwise the records of the pneumonia service were unfortunately deficient regarding the diabetes both in hospital and during the interval period. The pancreas weighed 90 gm. and was described as normal in gross appearance and consistency.

Pancreas.—Advanced fibrosis is present in all parts of the organ, invading the lobules in all directions. There has been much destruction of parenchyma. Some acini are still in various stages of involution and degeneration, but the majority contain considerable zymogen. Islands are very scarce, as though the great majority had been destroyed. Only a few of the remaining ones, however, are involved in the fibrosis. Most of those found appear normal and are free from vacuolation or "atrophy".

Remarks.—1. The case is one of the classical kind in which the destruction of parenchyma and loss of islands suffice to explain the diabetes on a quantitative basis. Even with this very marked anatomic loss, however, the diabetes was actually mild.

2. The absence of hydropic changes and the theoretical relations are discussed under the next case.

No. 8.

Clinical Summary.—For the record of this case the writer is indebted to Dr. Louis Jurist, who published an account of the initial condition, as observed up to 1909³. The patient was a Jewish merchant, aged 39 years when first seen in 1907. His mother was diabetic. He had had the ordinary childhood diseases, also typhoid fever when a boy, and pneumonia at 25. He was temperate in habits, ate plain food, took considerable exercise, and was not obese. In 1898 he first suffered from a severe epigastric pain, lasting through one night. Less severe attacks returned at long intervals during the ensuing years. In the summer of 1907 a severe attack required morphine for relief, and thereafter the seizures were more frequent. From Dec. 15 to 26, 1907, a series of particularly violent paroxysms of pain, with vomiting, temperature up to 100.2°, feeble irregular pulse, leukocytosis of 23,400, epigastric tenderness and distention, and the presence of a palpable mass extending from the epigastric and upper umbilical into the left lumbar region, led to the diagnosis of acute pancreatitis by Dr. Jurist and several consultants. On Dec. 28, through a left lumbar incision, dark necrotic material was evacuated from the pancreatic region, and some fat necroses were seen. On Jan. 8, 1908, a slough of pancreatic tissue measuring 4 x 2 x 2 cm. was removed from the wound, and on Jan. 31 another slough measuring 6 x 3½ x 3 cm. The patient gradually recovered, and normal utilization of food was demonstrated by fecal analyses. In the hospital there had been some albumin and casts in the urine, also traces of glycosuria. The latter cleared up imme-

diately and the former gradually, so that the patient seemed entirely well at the time of Dr. Jurist's published report in 1909.

Very wisely, the practice of occasional urinalyses was continued, and glycosuria was discovered several times in the latter part of 1909, with clear intervals between. This condition developed into an ordinary mild diabetes, and though the patient visited well known German resorts for treatment, he was careless of diet so that marked glycosuria was present almost continuously. Acetone was excreted almost constantly after 1911, but was generally slight and apparently never dangerous in amount. Traces of albumin and a few casts were also found regularly. After progressive loss of weight and increasing feebleness, death occurred in a stuporous condition in November, 1913. The 24-hour urine of the day preceding death amounted to 2840 cc., with 13.6 gm. nitrogen, 59 gm. glucose, and 0.68 gm. total acetone (0.35 gm. acetone plus diacetic, 0.33 gm. β -oxybutyric). Dr. Alonzo E. Taylor, who performed the analyses, estimated from the carbohydrate intake and sugar and nitrogen output that about 50 gm. of glucose must have been burned on this day. From this fact and the small acetone excretion he considered diabetic coma improbable and uremia a more probable cause of death.*

With much difficulty an autopsy was obtained about 12 hours after death, under circumstances not permitting of weighing of the pancreas remnant, which consisted of little more than the head of the gland, most of the tail and body having apparently been lost by sloughing. Microscopically, there was reported "moderate coarse infiltration of adipose tissue between and occasionally also penetrating lobules. Glandular acini appear normal and no constant changes are evident in islands of Langerhans; the latter, however, are very few in number (as is the case in the head of the pancreas). Occasionally a greatly hypertrophied island is seen but the hypertrophy is not constant. Such islands, however, when seen may fill an entire field (obj. 7, occ. 4, Spencer). It is impossible to demonstrate a definite uniform increase of connective tissue in any part of the gland, though its peritoneal surface shows some loose fibrous thickenings which penetrate somewhat between the lobules. No changes in the blood vessels." In addition, there was found a marked grade of chronic parenchymatous nephritis, and moderate fatty infiltration of the liver. Dr. Taylor kindly forwarded specimens of the pancreas for study.

Pancreas.—The slight or doubtful fibrosis and considerable infiltra-

* The large urine volume and nitrogen excretion may cast doubt on the diagnosis of uremia. Also, it is well known that in cases of diabetes with nephritis the acetone elimination may be slight though the tendency to acidosis is marked. This evidence may seem to favor diabetic coma. The following description of the pancreatic findings, however, is against diabetic coma and in favor of a mild diabetes terminated by some other cause of death. It is considered practically impossible that a diabetes should run an active course for several years and finally reach a degree of intensity sufficient to give rise to coma, without any discoverable hydropic degeneration of islands. Such anatomic evidence is highly important for decision in a doubtful case, if later investigators confirm this interpretation.

tion of adipose tissue are evident. The acini are normal, ranging in zymogen content from full to empty. Islands are scarce in some sections but apparently normal in others, and are free from fibrosis, "atrophy" or vacuolation. The specimens at hand do not show the hypertrophy of islands described by Dr. Taylor, but his mention of them creates the impression that these may have been the doubtful formations (perhaps derived from ducts) described by other writers, and probably most important as signs of a previous inflammation in the remnant of pancreas. Granule stains were made by W. B. Martin in the attempt to decide whether the apparently normal islands might be composed chiefly of alpha cells, but the tissue was not fresh enough for conclusive results. Other evidence, however, suffices to exclude this supposition.

REMARKS.

1. The possible instructiveness of a case of diabetes following partial pancreatectomy in man is evident. The requirement was partly fulfilled in this case, though there is a possible hereditary factor as well. It is also probable that the entire pancreas suffered more or less from inflammation, which was found in animal experiments to be a cause of diabetes. The fatty infiltration found at autopsy is probably an evidence of such injury, though the trivial fibrosis and relatively normal condition illustrate the high capacity of repair in this organ.

2. As hydropic degeneration occurs in every case of experimental diabetes of more than a few days' duration, there was a serious question why it should be absent in human cases in which hyperglycemia and glycosuria had existed unchecked for one to several years. This question was raised by cases such as No. 6, in which the diabetes seemed to arise chiefly from a functional change in the islands; also by No. 7, in which the quantitative destruction of islands by inflammation or fibrosis sufficed to account for the diabetes; and finally by the present case, in which vacuolation was absent though the diabetes actually followed a partial loss of the pancreas. The difference is not one between animals and man, for hydropic changes are sufficiently common in human diabetic autopsies. It is also not a difference between the diabetes following surgical resection of the pancreas and that which arises spontaneously, for the vacuolation was absent in this case after partial destruction of the human pancreas, and present in Krumbhaar's¹ dog with spontaneous diabetes. The difficulty

seemed so serious that the enunciation of any general theory of diabetic pathology appeared imprudent for several years. With further experience a childishly simple explanation was found in the fact that correlation is necessary between the clinical and the anatomic findings. Unchecked experimental diabetes in the dog runs a rapid course; as described in paper 1 of this series, total destruction of beta cells in the islands requires no more than 2 months, and death generally occurs within 3 or 4 months. Island cells ordinarily survive in the vacuolated condition only for a short period, perhaps a week, before going to pieces. Naturally, therefore, striking pictures of extensive hydropic changes are found in experimental diabetes and in the rapidly progressive human cases with intense symptoms. In human cases of an intermediate grade of severity and progressiveness, and in animals when the symptoms are partially controlled by diet so as to extend the downward progress over a long period, the visible vacuolation is much less. The mildest human cases, especially in elderly persons, are known to continue from 5 to 30 years before seriously impairing the subjective health. Visible active hydropic degeneration would necessarily involve total destruction of islands long before this, and accordingly visible vacuolation is usually not found in such cases, especially if death occurs from some other disorder. This does not mean that hydropic degeneration does not occur, for the tolerance nearly always falls gradually with neglect of diet even in the mildest and least progressive cases; this fall is ordinarily not due to any extraneous pathologic process, because it is prevented by dietary regulation; and it must therefore be attributed to a slow hydropic degeneration due to overtaxed function. If the diabetes finally turns severe and perhaps ends in coma, or if it is fanned into intensity by some intercurrent infection, correspondingly more active hydropic changes may be found at autopsy. Otherwise it must be rare that the death process of an occasional individual island cell comes under the view of the microscope, and the finding of even a single cell which is positively and characteristically vacuolated in freshly fixed tissue becomes therefore all the more important.

3. Apart from infectious or other accidents, the progressiveness of a case of diabetes depends upon the liability to hydropic degeneration of the islands from functional overstrain.

Two elements in severity may thus be distinguished; one the intensity of existing symptoms, or the limit of food tolerance at a given time; the other the inherent tendency to become better or worse with time. Equal hyperglycemia and glycosuria result in far more rapid downward progress in the average child than in the average elderly person. When glycosuria is kept absent by diet but hyperglycemia allowed to persist, nearly every youthful patient continues to progress downward, only somewhat more slowly than before; but some older diabetics maintain a stationary condition or actually improve. As the hydropic breakdown of island cells corresponds to the rate of clinical decline, some cause must exist for the different behavior of islands in different cases. The difference is not merely one of age, for some mild cases with little progressive tendency are found in the young and some severe and highly progressive cases in the old. It has also been impossible to correlate the progressiveness with the primary pathology, according as the diabetes might seem to arise from quantitative destruction of islands or from functional changes in them, or on any other anatomic basis. It has been shown heretofore that hydropic degeneration is not governed by glycosuria, as it sometimes occurs with hyperglycemia alone, nor by hyperglycemia, as it is not produced by sugar feeding or injections in non-diabetic animals and still occurs in diabetic animals whose blood sugar is kept at or below normal by phlorizin (paper 4). Two possibilities are therefore open; either that the unknown stimulus to over-function with excessive diets is stronger in some cases than in others, or (more probably) that the islands of some patients are more susceptible to breakdown from functional over-strain than those of some other patients. There are no indications of such individual differences between experimental dogs, and the reason for the marked variations among human cases in this respect is entirely unknown.

III. MICROSCOPIC DIAGNOSIS OF DIABETES.

Acknowledgment is due for the courtesy of a number of pathologists who kindly gave or loaned specimens for study. In order to test the feasibility of diagnosing diabetes with the microscope alone, requests were made for series of pancreas

specimens to be sent, representing mixed diabetic and non-diabetic cases, and marked only by numbers. Collections of this kind were first received from Dr. G. M. Mackenzie of the Pathology Department of the College of Physicians and Surgeons, New York, from Dr. Ralph H. Major, of the University of Kansas, and from Professor A. S. Warthin of the University of Michigan. It was possible to diagnose diabetes positively in some specimens of each series and doubtfully in others, but the percentage of errors in each instance was so high that the results were far from convincing. The chief causes of failure were first inexperience, which caused shrinkage due to formaldehyde fixation to be mistaken for vacuolation, and wrong interpretations of various forms of fibrosis etc.; second the inherent mildness of most of the cases represented, even when these had been described as severe by clinicians; third the admixture with examples of more or less marked pancreatitis, reported clinically as non-diabetic but, if so, differing from diabetic cases rather in the invisible island function than in the visible destruction; fourth the insufficient freshness of fixation in some cases; fifth the necessity of attempting diagnosis from one or rarely two slides, which does not afford a trustworthy judgment of the entire pancreas.

Similar series were sent later by Dr. E. W. Goodpasture from the Peter Bent Brigham Hospital, Boston, and by Dr. J. C. Aub from the Massachusetts General Hospital. The microscopic diagnoses in these cases were nearly one hundred per cent. correct. The reasons for the better success were first, greater experience, and second, the easier character of these two series. The diabetic cases were mostly of severe type, with hydropic degeneration or pronounced scarcity of islands, or both. The non-diabetic specimens were mostly of normal or only slightly altered pancreas tissue. Under these conditions there was room for doubt in very few cases.

For several months pancreatic specimens were sent by Drs. Lambert and Evans, of the pathological staff of the Presbyterian Hospital, New York, from all current autopsies obtained within 3 hours after death. Case No. 4 under section II (above) was discovered accidentally in this series.

Drs. Wilson and Horgan of the Mayo Clinic, Rochester, Minnesota, furnished a series of pancreatic specimens from cases of hyperthyroidism. The proportion showing more or less

fibrosis or other changes was rather high, but there was no vacuolation of islands or numerical reduction suggestive of diabetes. If any case of thyroid disorder happens to be associated with diabetes or even with hyperglycemia, it is believed that close attention should be given to the pancreas at autopsy before speculation is ventured concerning the etiology of the complication.

Some additional pancreatic material was obtained from the pneumonia, cardiac and other services of the Rockefeller Institute Hospital, a few of the cases (cf. No. 7 under section II) being also diabetic. Still more specimens from diabetic cases were sent in by a number of practicing physicians. The total series studied was thus brought up to more than a hundred diabetic cases and a larger number of non-diabetic cases.

The 15 cases described under sections I and II are believed to furnish types of practically all forms of diabetic pathology that exist, as judged by the present experience and also by reports in the literature (excepting acute pancreatitis, which may possibly be found with diabetes if specimens are obtained at the right stage).

IV. TECHNICAL AND DESCRIPTIVE DETAILS.

As already mentioned, fresh tissue is the first requirement for satisfactory study. Removal of the pancreas should be the first step in a diabetic autopsy. It is desirable that arrangements should be made for an immediate autopsy, so that the pancreas specimens can be in the fixative within half an hour after death, though material obtained within 3 or 4 hours is generally fit for study. The rate of autolysis varies widely, so that in tissue taken within half an hour the fine outlines of vacuolated cells have been partially lost (cf. Fig. 8), while in tissue 12 hours old the changes are sometimes distinct.

Zenker fluid is a good routine fixative, and the most recent information is that the full strength of acetic acid may be used without fear of dissolving the island cell granules. Other workers have obtained good results with other solutions, but the solution should always be one that will produce no shrinkage or artefacts. Ordinary formaldehyde is therefore bad for the purpose. It is preferable to take specimens in different bottles from the head, body and tail of the pancreas, to obtain

a judgment of the entire organ and its parts. The specimens may conveniently be of two kinds; one the ordinary size, to show the general architecture or pathology, and the other only a few millimeters in dimensions, for fine study of the islands or for special stains. The special stains require special fixatives, as described in paper 2 of this series. After imbedding in paraffin, the sections have generally in this series been stained with Mallory's methylene blue and eosin, though hematoxylin-eosin is also satisfactory. The sectioning and staining of these specimens (as also those in paper No. 1) were done by or under the direction of Miss Mary Holloway, and the microphotographs by Mr. L. B. Schmidt, to whom thanks are due for skill and courtesy.

A total of several dozen slides, representing several sections from several blocks from the different divisions of the gland, is the minimum for adequate study, and in special cases the numbers may run higher. The present series gives some examples of the marked differences between different portions of the same pancreas.

The illustrations are arranged not in order of cases but, like the animal series, to trace the development of various changes.

Fig. 1. — This is from a case of chronic nephritis, without diabetes. There is interacinar fibrosis; also the capsule and trabecular framework of the island are distinctly thickened. It is seen that the fibrosis in itself involves neither vacuolation nor "atrophy" of island cells. Two appearances in the island which distantly suggest vacuolated cells are nothing but corpuscles in capillaries. Particularly a lymphocyte in the middle of a capillary may under low powers of the microscope imitate hydropic change, but the high power quickly shows the mistake. It seems reasonable to suggest that suitable study may show a relation between the marked hyperglycemia of many cases of chronic nephritis or hypertension (even when classed clinically as non-diabetic) and these fibrous changes in the pancreas.

Figs. 2, 3, 4. — These are from case No. 4 of section II and from two other cases showing the first stages of hydropic degeneration. In Fig. 2, the prominent cell a little above the center of the island is vacuolated and swollen to as marked a degree as in an experimental animal. Its nucleus still re-

mains normal. The rest of the island is nearly normal. In Fig. 3, two vacuolated cells, one swollen much larger than the other, are seen near the lower right hand corner, and one at the top of the island. The island as a whole remains strictly normal. In Fig. 4 the changes are a little more advanced. Cells near the center of the island have gone to pieces, leaving a little debris. Several partially vacuolated cells are seen. Also many cells show what is called thinning of cytoplasm (or in special stains thinning of granulation), which is preliminary to actual vacuolation. All 3 figures are positively diagnostic of active diabetes, but yet such tissue has often been passed by pathologists as normal.

Figs. 5, 6 and 7 are from case No. 39 under section I. Fig. 5 is from the head, Fig. 6 from the body, and Fig. 7 from the tail of the pancreas. They represent successive advancing stages of hydropic degeneration.

Fig. 8 is from case No. 71 under section I. Maximal hydropic degeneration of islands, as extreme as anything ordinarily seen in animals, is shown under low power. This is from one of the few groups of large or hyperplastic islands found in the head and body of the pancreas, while in the tail islands were either absent or "atrophic". The outlines of some of the widely vacuolated cells are perfectly sharp, but in the majority the membranes have been lost or blurred by postmortem change, though the tissue was fresh.

Figs. 9 and 10 are from case No. 1 under section II. Both are from the tail of the pancreas, but yet as different as if from different patients. Fig. 9 shows one of the bands of interacinar fibrosis, and 3 islands which have undergone extensive hyalin transformation, but the remaining cells are as markedly hydropic as though no hyalin were present. Fig. 10 gives a low power view of tissue free from fibrosis or hyalin, with 2 islands in which a majority of the cells are in early or late stages of hydropic degeneration.

Fig. 11 is from the tail of the pancreas in case No. 39 under section I. It illustrates one of the large or hyperplastic islands found in places throughout the pancreas. The sprinkling of round cells, connective tissue cells and shrivelled island cells with pyknotic nuclei, among normal and vacuolated island cells, is interpreted as probably an early or partial "atrophy".

Fig. 12 is from case No. 8 under section I, and represents

one form of advanced "atrophy". Islands are plentiful, but a complete or nearly complete absence of function was indicated by the trivial food tolerance. Fibrosis is barely perceptible or absent. Nevertheless the islands, like accumulations of lymphocytes, stand out strikingly against the acinar tissue by the dense dark staining of their shrunken cytoplasm and pyknotic nuclei. The acini are nearly empty of zymogen, as not uncommonly found in cachexia, but are not otherwise altered.

Fig. 13 is from case No. 4 under section I. The wide area under low power is shown as illustrative of the absence of normal islands. Along the left side are 4 islands in the most extreme state of "atrophy". One is barely distinguishable in the upper left corner; the other 3, lower down, appear plainly. The trabecular and capillary framework is fibrosed until it fills the greater part of the island area. The island cells are extremely shrunken, but do not take an excessively dark stain.

Fig. 14 is from a different part of the same pancreas, and shows the "pseudo-islands" which are interpreted as probably formed by duct proliferations. Those on the left more nearly resemble acinar tissue, but the cells are in columns. Particularly the one on the right imitates the form of an island, but the cells have the same characters, namely a fuller and denser protoplasmic body and a deeper and more basophilic stain than true island cells.

CONCLUSIONS.

1. The pancreas in every case of diabetes in this series has borne marks of infectious or toxic damage as the presumable cause of the diabetes. Even when the general architecture is normal except for an apparently trivial fibrosis or fatty or other change, this may still be important as the remains from an original acute pancreatitis in which the diabetes took origin. In most cases these changes are fairly plain, but in a few instances careful search through many sections is necessary to discover the slight alterations in organs which are reported as "practically normal" in the ordinary pathological examination. The difference between a true chronic pancreatitis and the mere healed scars of acute lesions must be borne in mind in such a study.

2. In some cases the diabetes seems explainable by the

quantitative loss of islands or visible signs of their injury in the form of fibrosis, hyalin deposit, "atrophy", etc. In other cases either the existence or the severity of diabetes must be partly or wholly explained by the assumption of a functional deficiency in normal appearing island cells. The possibility of such functional injury by inflammation was shown experimentally in paper 6.

3. The 4 hereditary cases (Nos. 4, 39 and 73, Section I; No. 2, Section II) have shown the same signs of infectious or toxic etiology as the others of the series. As far as the pathologic findings are concerned the hereditary are indistinguishable from the non-hereditary cases, and the assumption of functional deficiency is not required in one group any more than in the other. A warning must be voiced, however, that the clinical record can seldom if ever furnish decisive evidence for classifying any case as non-hereditary⁵.

4. Hydropic degeneration is demonstrable in the human pancreas whenever diabetic symptoms have been sufficiently intense and prolonged, but is ordinarily missed in the mildest cases. It is to be interpreted as an anatomic breakdown of island cells by over-stimulation of their internal secretory function on excessive diet, as in animals. It furnishes a clear explanation of the progressive decline of assimilative power which is known to result from such diets. The reason for the widely different susceptibility of different patients to downward progress clinically and to hydropic degeneration of islands anatomically is unknown. The quantitative deficit of islands at autopsy is frequently not due entirely to the primary cause of the diabetes but largely to the hydropic degeneration resulting from the diabetes.

5. The great majority of cases of severe diabetes can be diagnosed microscopically by either hydropic degeneration, or deficit or visible injuries of islands, or both. It is also possible, with some allowances for functional variations, to predict the autopsy findings from the clinical record. When a patient dies with intense diabetic symptoms, the finding of hydropic changes can be definitely predicted. When the case is one of the extremely severe type, in which symptoms have been strictly abolished for a long time but the patient has gradually starved to death for want of ability to acquire tolerance for any living diet, it is to be anticipated that islands will be

found extremely few, or fibrosed or "atrophic". Simple functional deficiency probably never suffices to cause diabetes of fatal severity; and when there is an abundance of normal looking islands or when a diagnosis is doubtful between diabetes and any non-diabetogenic lesion, it may be concluded that death was probably due to some complication or accident.

6. The pathology bears an important relation to the treatment and prognosis of diabetes. While a true chronic pancreatitis or recurrence of acute or subacute attacks must be considered in some cases, the pathologic findings give the impression that from the standpoint of primary etiology the diabetic pancreas in most cases represents a burn-out conflagration, and that the chief or sole cause of aggravation of the condition lies in hydropic degeneration of islands. This interpretation alters the former conception of diabetes as an inherently progressive disease, and affords ground for regarding the average case as the consequence of damage of a vital organ, which is in danger of further injury chiefly or solely from functional over-strain. Clinical evidence to date corroborates this view in showing that by sufficiently thorough dietary control the downward progress of most cases of diabetes is either halted or almost indefinitely delayed.

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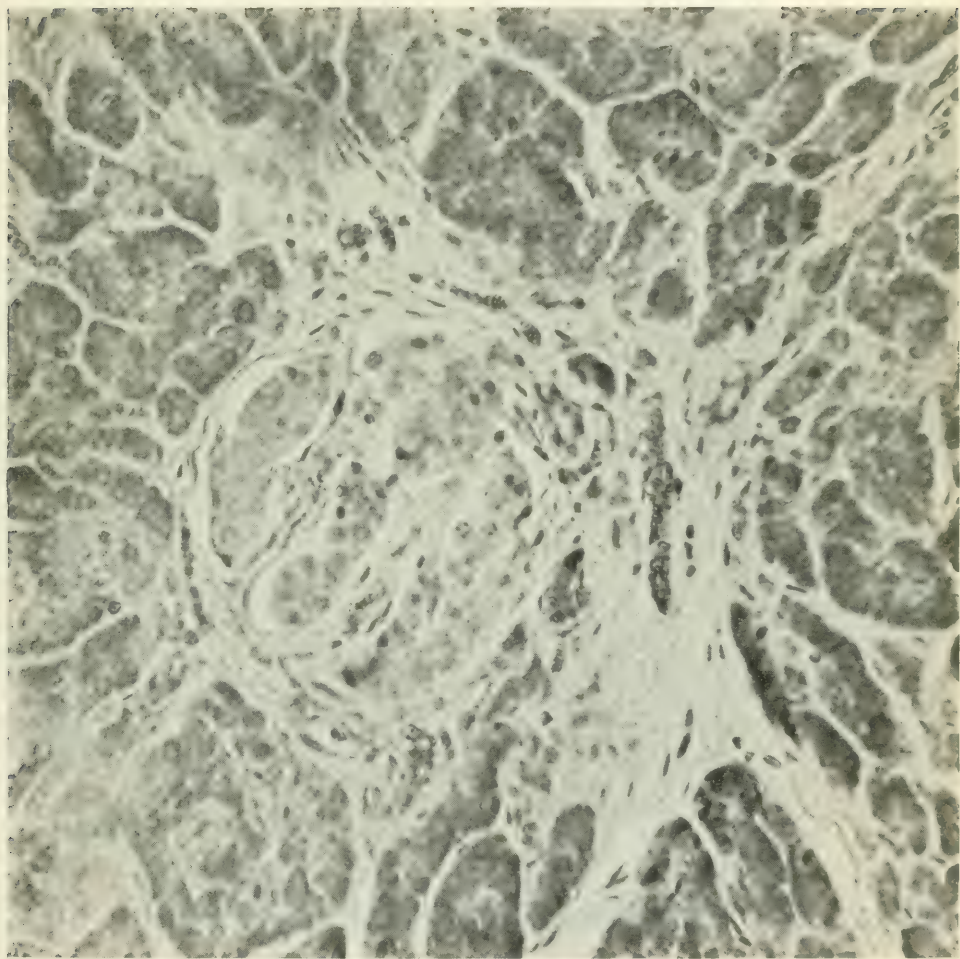


FIG. 1.

× 440.

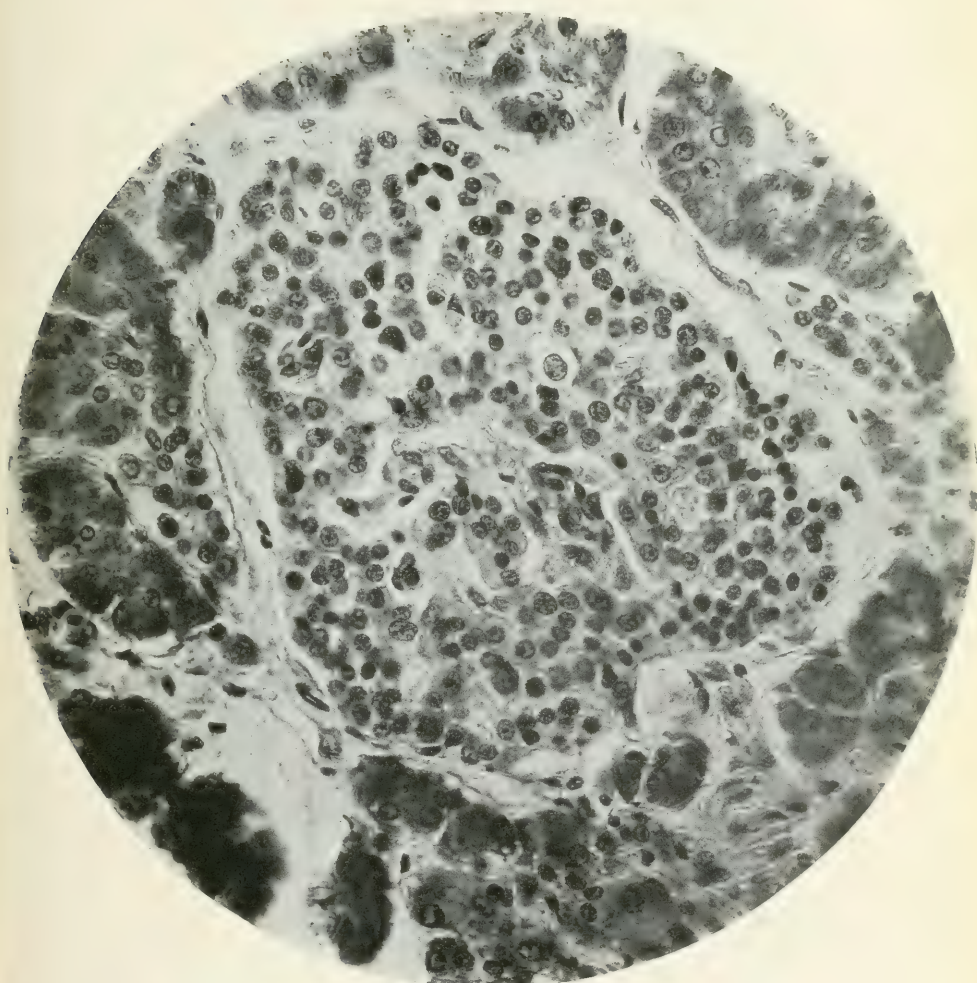


FIG. 2.

× 550.

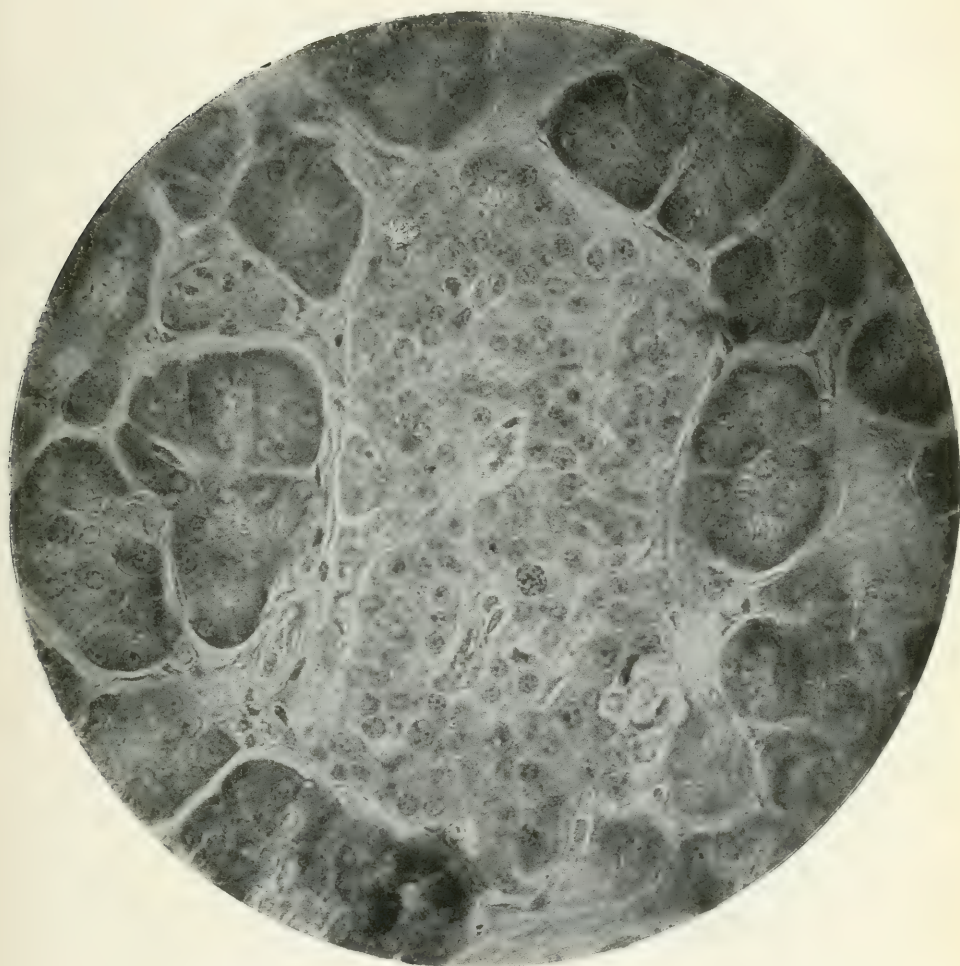


FIG. 3.

× 550.

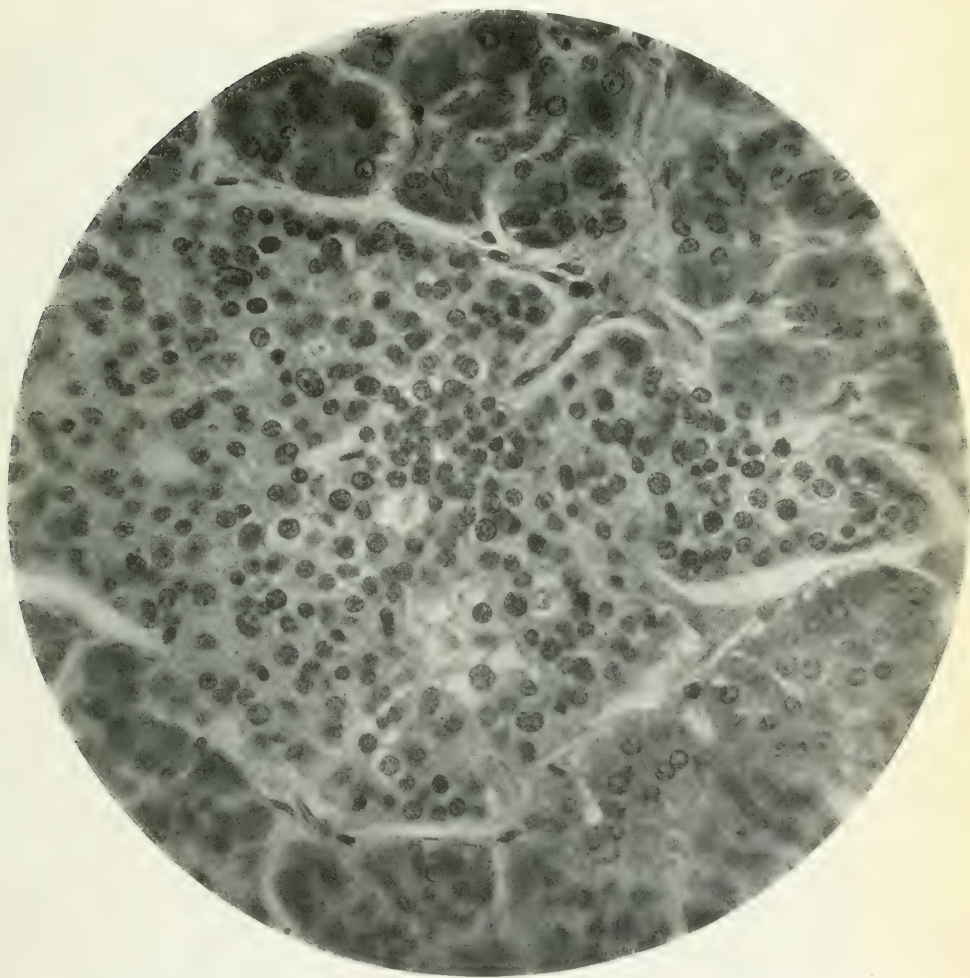


FIG. 4.

× 550.

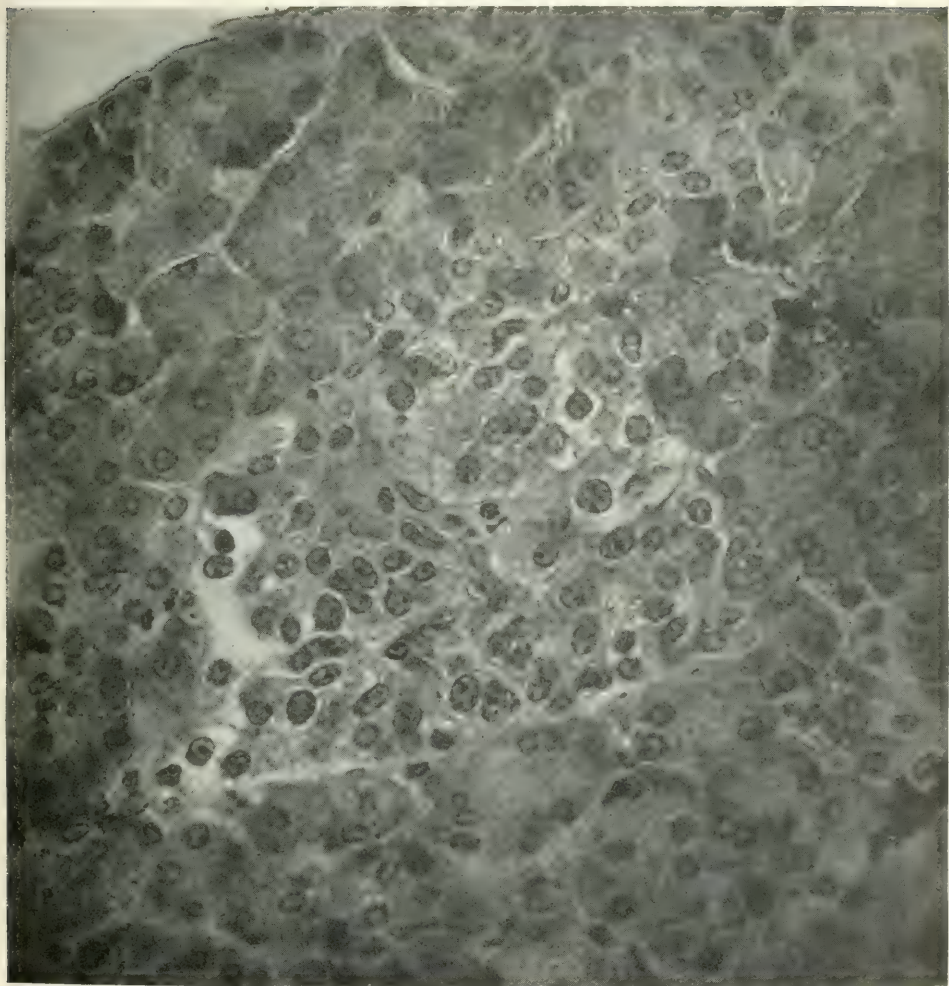


FIG. 5.

× 720.

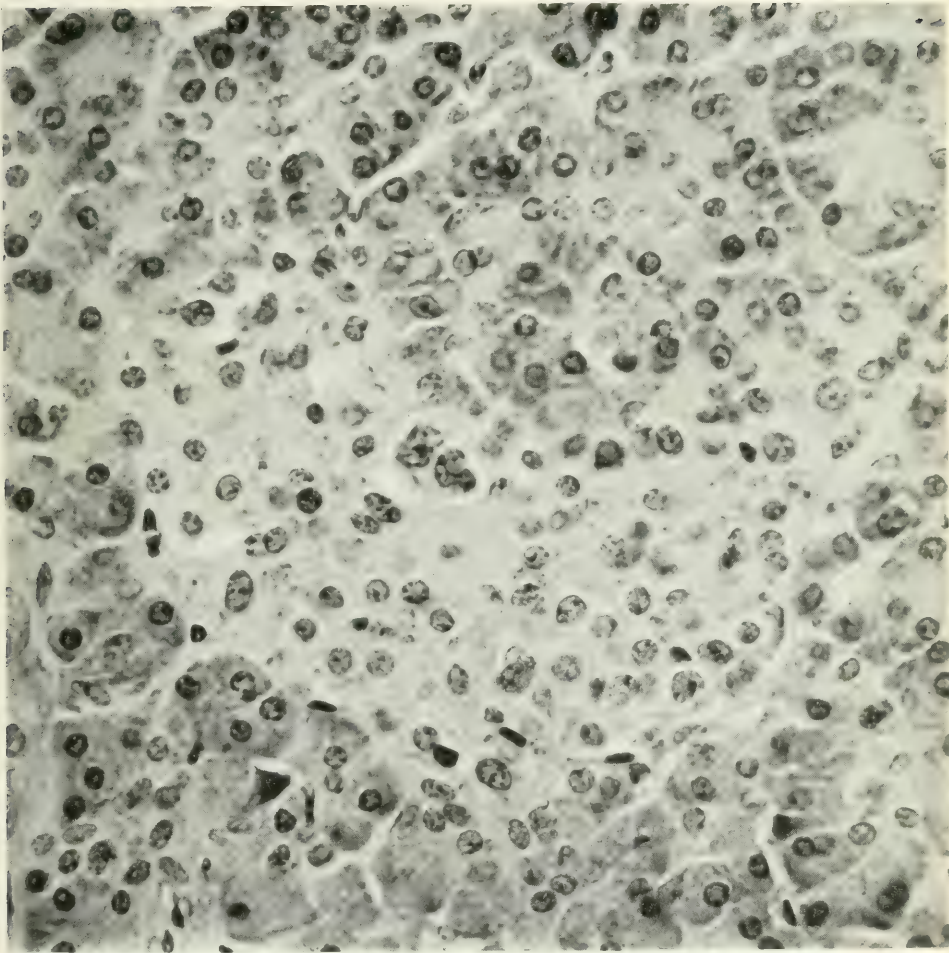


FIG. 6.

× 720.

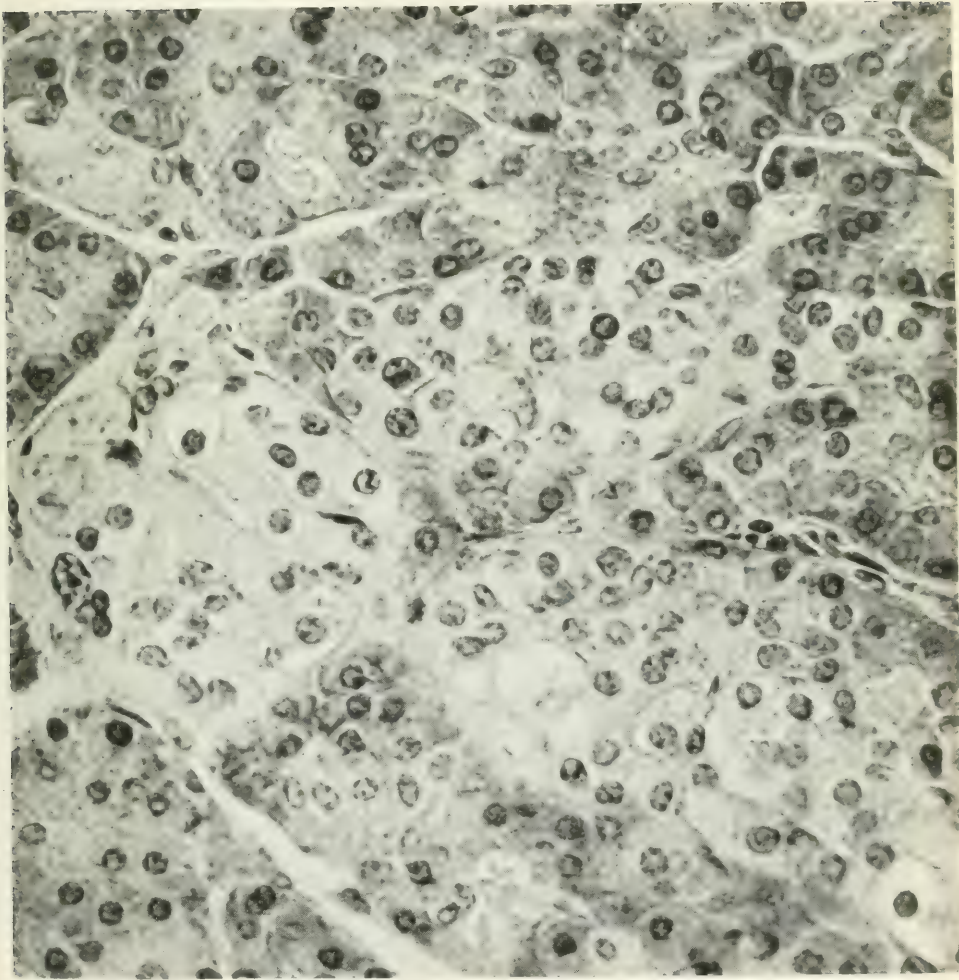


FIG. 7.

× 720.

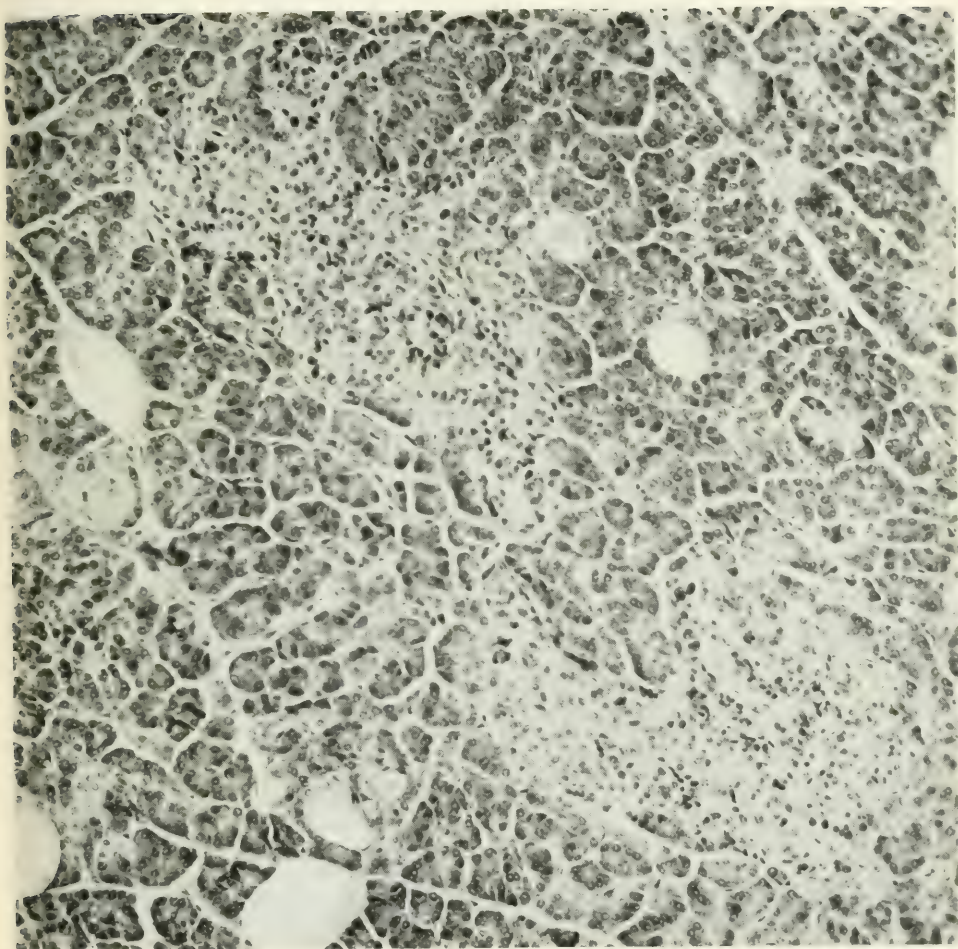


FIG. 8.

× 240.

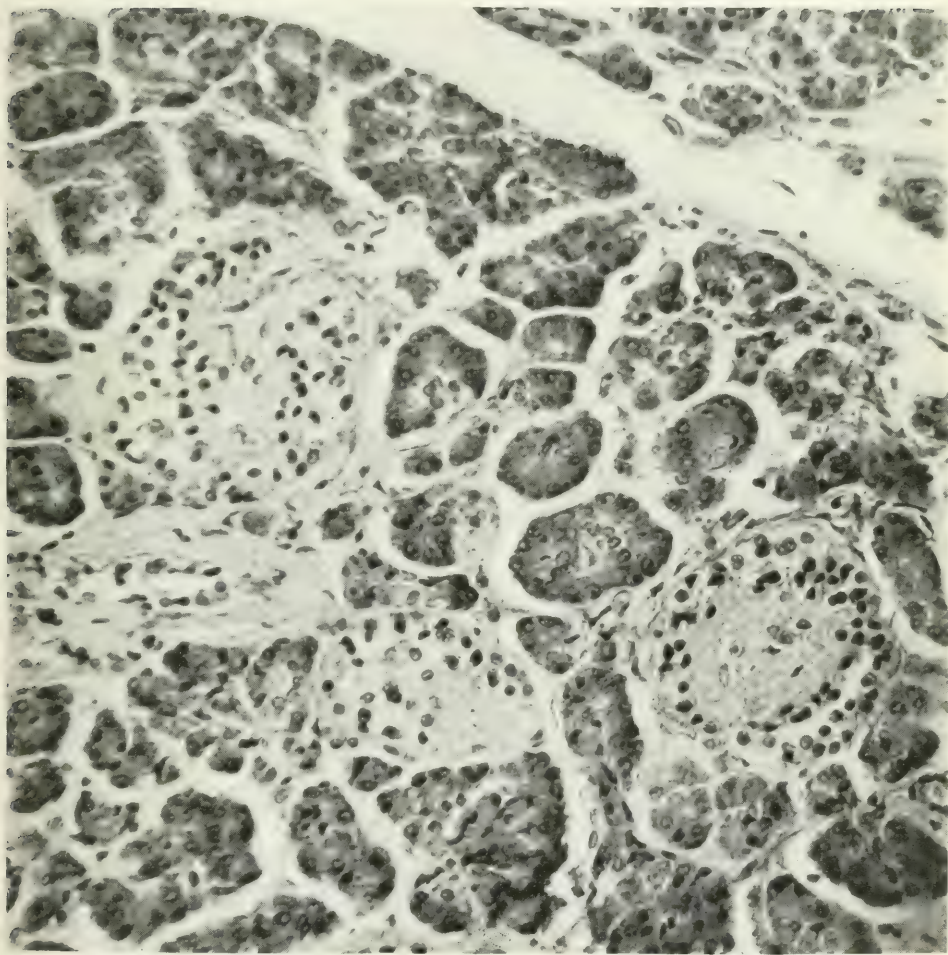
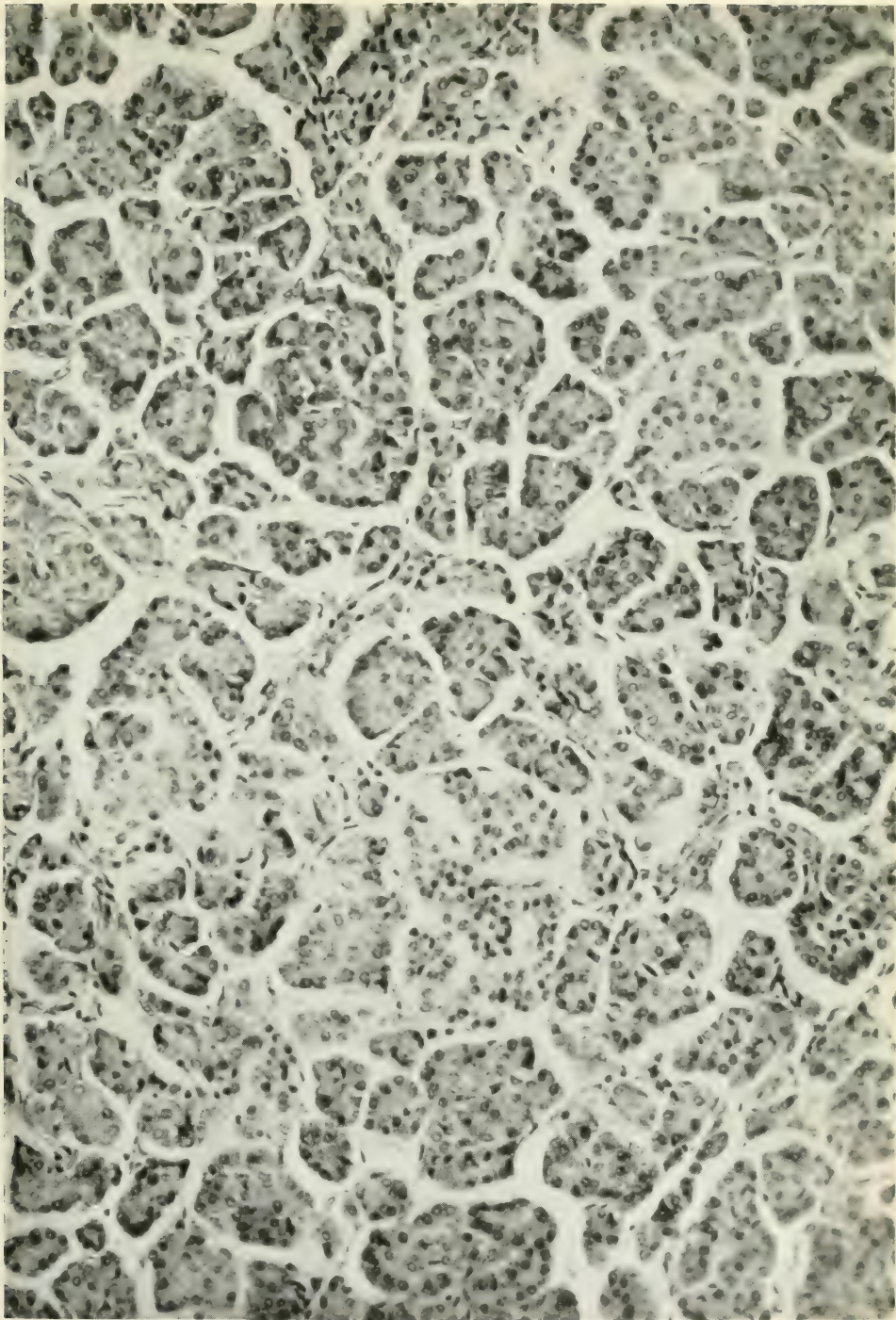


FIG. 9.



× 240.

FIG. 10.

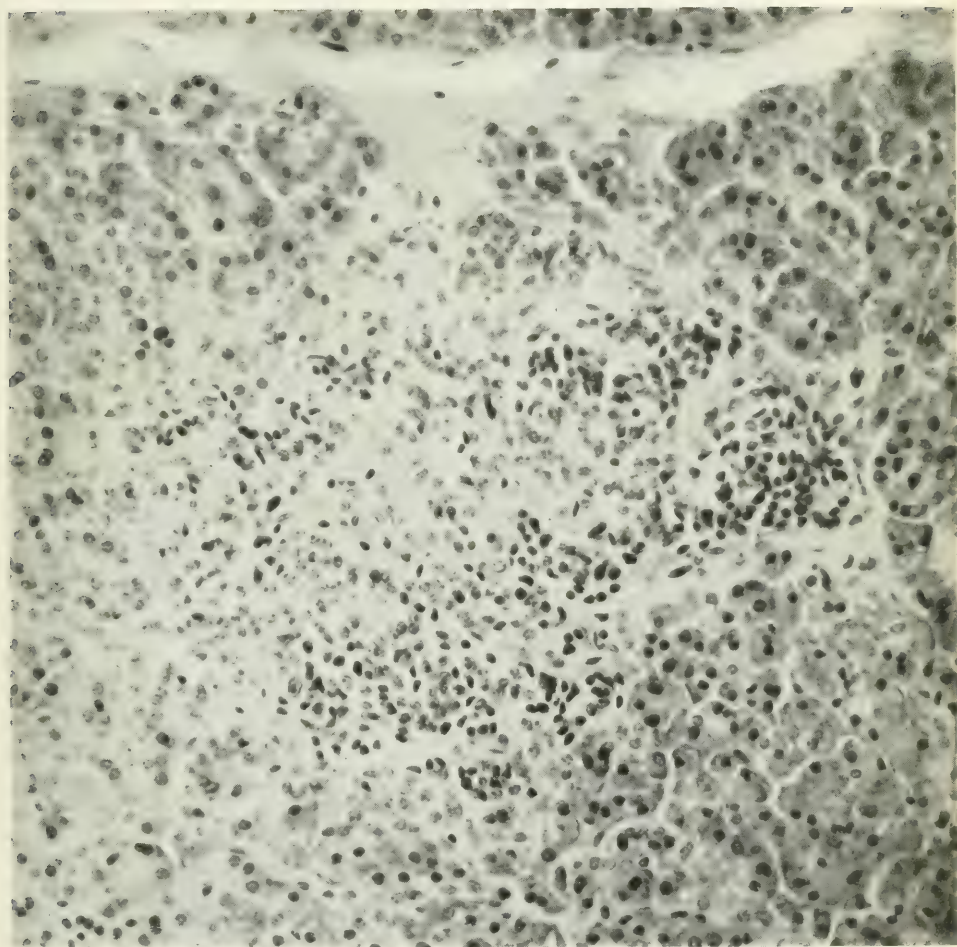


FIG. 11.

× 440.



FIG. 12.

× 240.

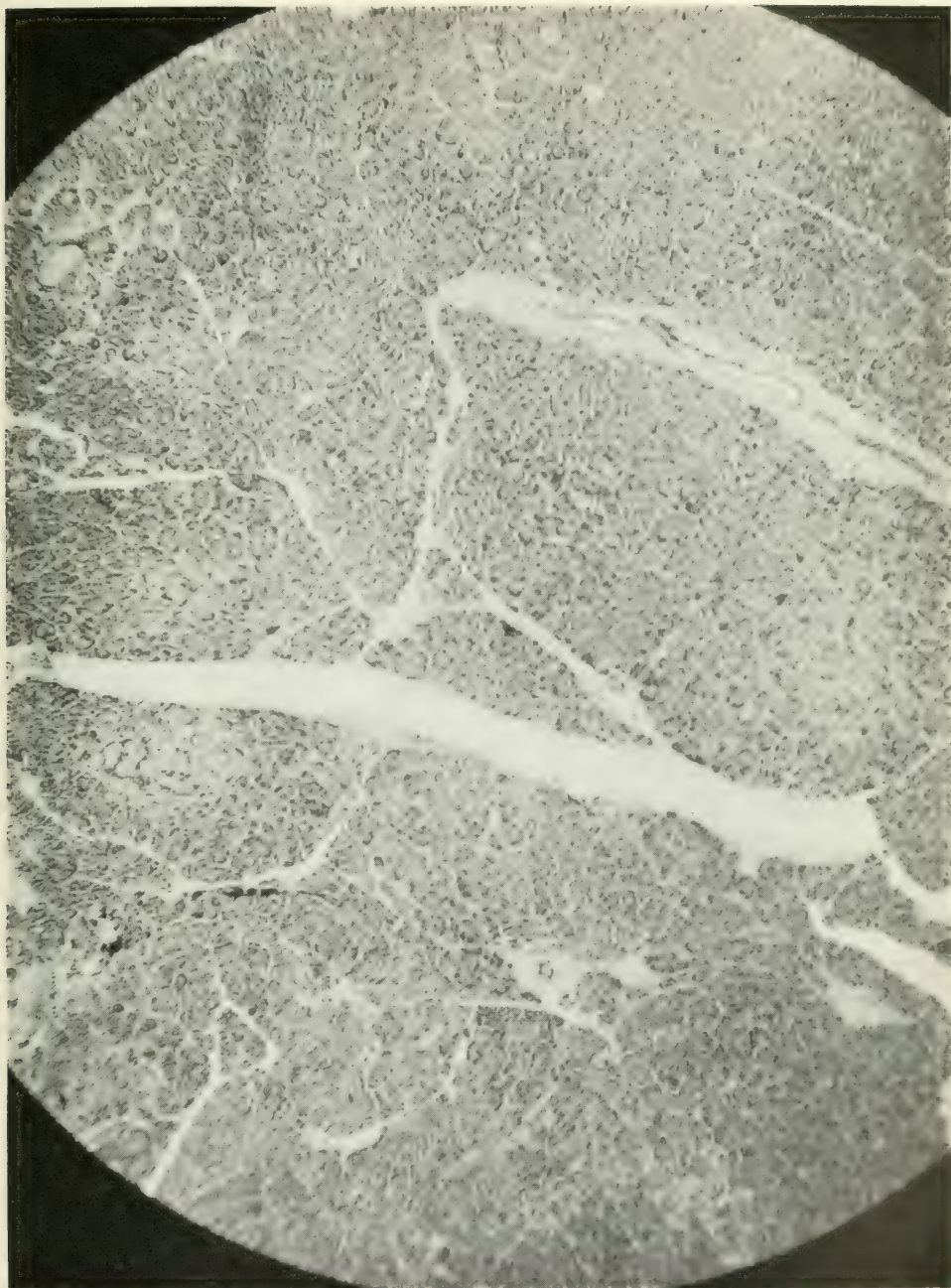


FIG. 13.

× 100.

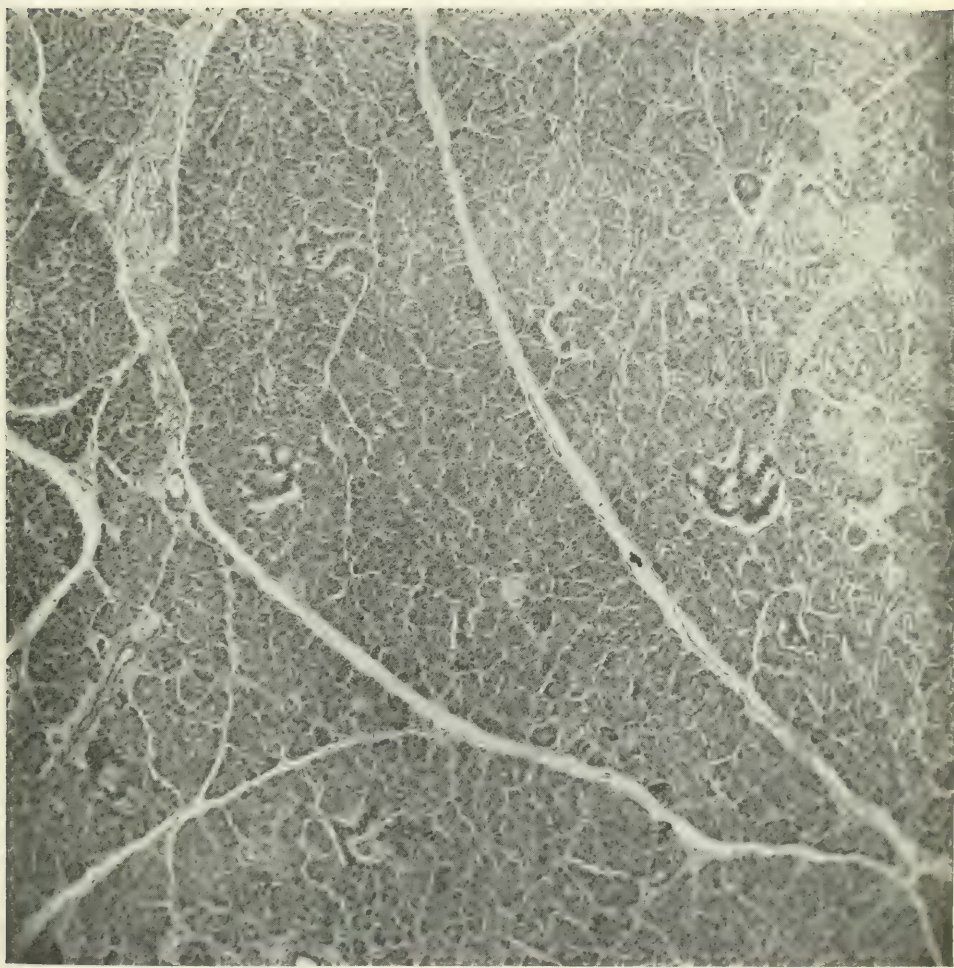


FIG. 14.

× 150.

EXPERIMENTAL STUDIES IN DIABETES

SERIES III. THE PATHOLOGY OF DIABETES.

8. THE MICROSCOPIC PATHOLOGY OF THE PANCREAS IN 570 UNSELECTED HOSPITAL CASES.

BY FREDERICK M. ALLEN.

From the Physiatrie Institute, Morristown, New Jersey.

It seemed highly desirable that before the responsibility was undertaken of proposing the criteria suggested in the preceding paper for the microscopic recognition of diabetes, a more adequate practical test should be made by taking the mixed autopsy specimens of a large hospital and attempting to distinguish the diabetic from the non-diabetic cases. Also, the theory of the etiology of diabetes here developed called for further observations to supplement the scanty existing statistics of the general incidence of pancreatic lesions.

After the writer had left the Rockefeller Institute, the desired opportunity was afforded through the courtesy of Professor James W. Jobling and Dr. A. A. Eggstein of the pathology department of the Presbyterian Hospital, New York. Sections, mostly Zenker fixed and hematoxylin-eosin stained, were loaned with only the series number of the hospital collection marked on each slide. After completion of the study the list of microscopic diagnoses was compared with the hospital records. The fact that generally only one slide was available from each case imposed a certain limitation in the recognition of diabetes and also affected the findings in other respects. For example, the number of focal necroses is doubtless much smaller than might have been revealed by thorough search of each pancreas, and the same is true to less extent of other lesions. In general, the attempt was made to err on the side of conservatism in recording only unquestionable changes as pathological. The 21 diabetic cases are first presented as in-

dividuals, and then the 549 non-diabetic cases in clinical groups.

21 CASES OF DIABETES.

The cases will be taken up serially according to the autopsy numbers of the hospital, and the grounds for diagnosis given in each.

Case No. 7830 was recorded by the writer as "Normal pancreas; no diabetes", and case No. 8059 as "Slight pancreatitis; no diabetes", though in the hospital records the former was described as atrophy of the pancreas with hyalin degeneration of islands of Langerhans, and the latter as a case of marked hemochromatosis. Later inspection of the sections easily confirmed these changes, which were sufficient to afford a diagnosis of diabetes without difficulty, and it was evident that in some way slides were confused in the handling of the long series, introducing an accidental error which has no bearing on the real question of diagnosis.

Case No. 7900. Age 38 years. Autopsy 6 hours post mortem. Diabetes, chronic interstitial nephritis, cholelithiasis, chronic cholecystitis. There was slight fibrosis and fatty replacement of parenchyma. Islands were strikingly scarce, but free from vacuolation when found. The microscopic diagnosis of "possible mild diabetes" was therefore made. A greater number of sections would have afforded greater certainty, but such scarcity of islands is seldom seen without diabetes.

Case No. 7997. Age 57 years. Autopsy while body was warm. Diabetes, chronic interstitial nephritis, amputation of left leg (gangrene). It was stated that the body was that of a well developed, well nourished man. The record also mentioned chronic interacinar pancreatitis and hypertrophy and regeneration of islands of Langerhans. The number of islands present and the freedom from vacuolation created doubts for the microscopic diagnosis, which was therefore written, "Probably no diabetes, though it is possible".

Case No. 8091. Age 47 years. Autopsy 2 hours post mortem. Diabetes, chronic interstitial nephritis, general arteriosclerosis, incipient acute broncho-pneumonia. 6 slides of pancreas were available, which showed extensive diffuse fibrosis, including primary fibrosis of some islands, a markedly subnormal number of islands, "atrophy" in a large proportion of islands, and vacuolation of a few cells in islands free from fibrosis and "atrophy". The positive diagnosis of diabetes was therefore easy.

Case No. 8146. Age 52 years. Diabetes, general and cerebral arteriosclerosis, thrombosis of left axillary vein, fibrinous pleurisy, tuberculosis upper lobe right lung. There was slight fibrosis and an occasional sprinkling of fat cells in the pancreas, also slight fibrosis and hyalin formation in some islands. In some areas islands were distinct-

ly scarce, and the total number seemed reduced. No positive vacuolation was found. The microscopic diagnosis was therefore limited to "diabetes possible".

Case No. 8194. Age 76 years. Diabetes, chronic cardiac valvular disease with hypertrophy and dilatation, chronic diffuse nephritis, atheroma of aorta and coronary arteries, hydrothorax, chronic pulmonary tuberculosis, hypertrophy of prostate. Three slides were available, showing slight to moderate fibrosis, never involving islands primarily, but evidently reducing their number by destruction of entire lobules. No vacuolation or "atrophy" of islands was seen, and the question was whether the injury of islands was sufficient to produce mild diabetes. The diagnosis was therefore limited to "mild diabetes possible".

Case No. 8463. Age 27 years. Diabetes mellitus. The pancreas showed slight diffuse fibrosis, with little apparent damage of islands, which were present in fair number but small size. Hemorrhage was found in one island. The diagnosis hung upon the question of vacuolation in island cells, and the postmortem changes were sufficient to render these doubtful. The two slides of this tissue were inadvertently examined apart. In one of them the vacuolation was regarded as probably genuine, and the diagnosis recorded as "probably diabetes", while in the other they were interpreted as probably artefacts and the diagnosis recorded as "probably not diabetes".

Case No. 8471. Age 38 years. Diabetes mellitus. Subpleural hemorrhage. Cystic kidney. The pancreas showed marked interlobular pancreatitis, sometimes penetrating the lobules but not the islands. There was marked involution and degeneration of the acinar tissue, but on the whole the islands seemed fairly well preserved. Neither "atrophy" nor vacuolation was positive in them. The diagnosis turned upon the interpretation of clear areas which were plainly evident in some islands, but it was concluded that they were probably postmortem changes and not true hydropic degeneration. The diagnosis was therefore written "Diabetes possible but not probable".

Case No. 8513. Age 55 years. Autopsy 3 hours postmortem. Caruncle of back of neck. Adherent pericardium. Obesity. Fibrosis was so slight that in the average autopsy the pancreas would be passed as normal. Notwithstanding the obesity mentioned, there was no adipose tissue seen in the pancreas. Several hemorrhages into islands were noticeable. Islands were abundant, large, and apparently normal, except for a few typically hydropic cells which established the positive diagnosis of diabetes in a case which had not been supposed to be diabetic, as described in the preceding paper (case 4, Section II).

Case No. 8640. Age 55 years. Autopsy 17½ hours post mortem. Diabetes mellitus of 17 years duration, carcinoma of uterus, chronic glomerulonephritis, general arteriosclerosis, fatty heart, chronic pulmonary tuberculosis, general anasarca. The pancreas showed slight

diffuse fibrosis, with involution and degeneration to a disproportionately advanced degree. Islands were probably a little reduced in number, and showed slight or often doubtful "atrophy", fibrosis and hyalin formation. The question was whether these changes were extensive enough to signify diabetes. The judgment formed was expressed in the diagnosis, "Probably not diabetic".

Case No. 8669. Diabetes mellitus, nephrolithiasis, hydronephrosis. Postmortem change was so great that it was barely possible to make out slight fibrosis and fatty infiltration in the pancreas, and marked scarcity and small size of islands. Nevertheless these appearances, found in 3 sections (head, body and tail) sufficed for the diagnosis, "Probable diabetes".

Case No. 8679. Age 36 years. Autopsy 17 hours post mortem. Diabetes mellitus (2 years), lobar pneumonia, acute fibrinous pleurisy, glycogenic infiltration of kidney. The pancreas showed a delicate diffuse fibrosis, including slight fibrosis of some islands. The number of islands appeared to be distinctly though not extremely subnormal. Judgment concerning vacuolation was impossible because of post-mortem changes. The diagnosis was therefore written, "Diabetes suspected from fewness of islands and type of pancreatitis".

Case No. 8693. Age 28 years. Autopsy 3 hours post mortem. Diabetes mellitus, general anasarca, hydrothorax, ascites. Several slides of pancreas showed slight to moderate fibrosis, both inter- and intra-lobular, with some edema and round cell infiltration of the septa. The acini were mostly empty or involuted. The islands were not involved in the fibrosis, but appeared moderately reduced in number. Their cells were mostly small, dense and closely clumped, but in view of the atrophic appearance of the acini it was questionable whether any significance could be attached to this appearance. Search revealed one island cell in the body of the pancreas which seemed definitely vacuolated. The diagnosis was therefore written, "Probable diabetes".

Case No. 8725. Age 67 years. Autopsy 14 hours post mortem. Prostatectomy (for hypertrophy), acute and chronic cystitis, arteriosclerosis (general, but especially of aorta, coronaries, splanchnics, and renals), chronic myocarditis. Glycosuria was found at admission on June 16; there were no subsequent urinalyses up to death on June 23. The pancreas was reported normal in the routine autopsy record. The writer's description read, "Slight pancreatitis. Islands numerous, normal; some appearances like exhaustion are evidently postmortem change. No diabetes".

Case No. 8742. Mulatto, aged 52 years. Autopsy 4 hours post mortem. Diabetes mellitus (3½ years). Wassermann negative. General arteriosclerosis, gangrene right leg, multiple infarcts of lungs; chronic passive congestion of viscera, hydrothorax, secondary anemia. Two slides of pancreas were available, both showing slight diffuse fibrosis of parenchyma including the islands. Islands were scarce and small in one

section, larger and more numerous in the other, one being gigantic. The great majority of islands showed unmistakable hydropic degeneration in one to several cells. The positive diagnosis of diabetes was therefore made.

Case No. 8745. Diabetes, obesity, cholelithiasis, furunculosis. There was fibrosis of moderate to severe grade and considerable fatty replacement in the pancreas, with acini poorly filled and frequently in involution. Islands seemed to be reduced in number, slightly in some areas, markedly in others. Fibrosis was present in them, but to much less degree than in the acinar tissue. Postmortem changes interfered with the study and prevented judgment concerning hydropic degeneration. The microscopic diagnosis therefore had to be limited to "Diabetes possible".

Case No. 8750. Age 65 years. Autopsy 12 hours post mortem. Diabetes mellitus (3 years), carcinoma of gall-bladder with metastases in pylorus, retroperitoneal and mesenteric glands, cholelithiasis, ascites, general arteriosclerosis, lobular pneumonia. The pancreas showed spots of autolysis, uncertain whether ante- or post-mortem in origin. The organ otherwise was described as normal in the autopsy report. The writer's description read, "Slight pancreatitis. Islands normal. No diabetes". Hydropic degeneration could scarcely have been expected in a case of mild diabetes in which there was vomiting for 2 weeks before death.

Case No. 8758. Age 48 years. Autopsy 16 hours post mortem. Diabetes mellitus (2 years), gangrene of leg and amputation, arteriosclerosis (especially iliacs and femorals), suppurative nephritis. Four slides of pancreas showed slight to moderate intralobular fibrosis, also considerable adipose tissue scattered between and through lobules. Islands were in general not involved in the fibrosis, but seemed slightly reduced in number. A minority of them showed apparent vacuolation of a few cells, but owing to postmortem changes it remained uncertain whether these were true hydropic degeneration or artefact. The diagnosis therefore had to be limited to "Diabetes possible".

Case No. 8759. Diabetes mellitus (2¾ years), arteriosclerosis, lobular pneumonia. No glycosuria during 1 week in hospital; coma nevertheless. Four slides were available, showing slight to moderate pancreatitis, patchy in distribution. A significant feature seemed to be that islands were not apparently involved to any important extent in the fibrosis, but yet were markedly scarce, suggesting a possible loss through hydropic degeneration. No vacuolation was visible, and a positive diagnosis of diabetes was based solely upon the scarcity of islands.

Case No. 8770. Diabetes (began acutely with vomiting and polyuria on a definite day), decubitus ulcers, lobular pneumonia. The autopsy report mentioned extreme scarcity of islands, and small stellate scars interpretable as remains of destroyed islands. Otherwise fibrosis in either acinar tissue or islands was trivial or doubtful. Most of the

islands had the shrivelled appearance of typical "atrophy". In a few islands free from this change, a minority of cells showed unmistakable hydropic degeneration. The diagnosis of diabetes was therefore positive.

DISCUSSION OF DIABETIC CASES.

1. *Age.* Of 15 cases in which the ages were ascertained, 2 were in the third decade, 3 in the fourth decade, 2 in the fifth decade, 5 in the sixth decade, 2 in the seventh decade, and 1 in the eighth decade of life.

2. *Associated conditions.* Attention has long been given to the association of obesity and of tuberculosis with diabetes. Cholelithiasis and syphilis are of interest as possible causes. In connection with the theory of infectious origin, attention was paid to the association with cardiovascular disease and nephritis, for information as to how often an infection which strikes one organ may also involve others. In this series of 21 fatal cases of diabetes, there was a record of syphilis in none, cholelithiasis in 3, obesity in 3, tuberculosis in 3, heart disease in 3, nephritis in 7, and arteriosclerosis in 11.

3. *Pancreatic changes.* (a) *Fibrosis.* Some degree of fibrosis was found in all 21 diabetic cases. This was advanced or severe in degree in only 5 cases (Nos. 7830, 8059, 8091, 8471, 8745), and in general was less than in the 4 cases of pancreatitis listed in the non-diabetic series. In 2 cases (Nos. 8725, 8750) it was so slight that it was not mentioned in the routine autopsy report, and in 2 others (Nos. 8513, 8770) close examination was required to recognize it.

(b) *Fatty infiltration,* or the replacement of larger or smaller areas of parenchyma by adipose tissue, was observed in 1 case (No. 8745) with obesity, and in 4 cases (Nos. 7900, 8146, 8669, 8758) without obesity. In 2 cases (Nos. 8513, 8640) there was obesity without fat in the pancreas.

(c) *Hyalin in islands.* This was present in 3 cases (Nos. 7830, 8146, 8640).

(d) *Hemorrhages in islands.* These were observed in 2 cases (Nos. 8463, 8513).

(e) *Number of islands.* Judgment was necessarily uncertain when based on only one or a few slides. Nevertheless islands were found markedly and significantly scarce in 6 cases (Nos. 7900, 8091, 8669, 8745, 8759, 8770). The scarcity seemed slight but still suggestive in 7 cases (Nos. 8146, 8194,

8463, 8679, 8693, 8742, 8758). There was no suspicion of a reduction of number in 2 cases (Nos. 8725, 8750), and in 1 case (No. 8513) the abundance of islands was noticeable.

(f) Weichselbaum's "atrophy". This picture of shrinkage of cytoplasm and pyknosis of nuclei of island cells was found in 4 cases (Nos. 8091, 8640, 8693, 8770).

(g) Hydropic degeneration. Vacuolation of island cells was unmistakable in 3 cases (Nos. 8091, 8513, 8742). It was evidently present but blurred by postmortem change in at least 5 cases (Nos. 8463, 8471, 8693, 8725, 8758).

4. *Progressive character of lesions.* It is obviously impossible to decide concerning the possible progressiveness of hyalin or "atrophic" changes. Even when an active cellular infiltration accompanies fibrosis, it is impossible to predict whether the inflammation will progress or recede. Attention may be called to two points. (a) The degree of existent pancreatitis does not run parallel to the clinical progressiveness as known from clinical experience. For example, marked pancreatitis was present in cases No. 7997 (57 years), No. 8194 (76 years), and 8758 (48 years), at ages when diabetes is usually but little progressive, and also in No. 8693 (28 years), when the progressiveness is usually greater. Likewise there was little fibrosis or apparent damage of islands in the elderly cases No. 8725 (67 years) and No. 8750 (65 years), and also in the youthful case No. 8463 (27 years). (b) In occasional cases the pathological picture agrees with the clinical history in indicating the origin of the diabetes in an acute pancreatitis, of which the existing fibrosis represents only the healed scars and not a chronic or progressive process at all. Numerous other cases are capable of a similar interpretation. The hydropic degeneration is known to be progressive but is entirely dependent upon diet.

5. *Diagnosis of diabetes.* Barring the 2 cases (Nos. 7830 and 8059) in which the wrong slides were evidently taken, in the remaining 19 cases the diagnosis was made as follows: diabetes positive, 5 cases; diabetes possible or questioned, 12 cases; negative, 2 cases. The diagnostic signs in the order of their importance were the following: (a) Hydropic degeneration. This when present was the most conclusive proof, and decided the majority of the positive cases. The positive list could have been appreciably extended except for post-

mortem changes which rendered the appearances of vacuolation doubtful. (b) Scarcity of islands. Anatomic deficiency of island tissue was noticeable in the majority of these specimens and doubtless is present in the majority of all diabetic cases at autopsy. Frequently the scarcity is obvious enough that judgment can be risked on the examination of a single slide. A greater number of sections would have settled doubts of the diagnosis in several cases of this series. The reduction in number and size of islands may be due either to inflammatory destruction or hydropic degeneration. The 3 cases with apparently normal numbers of islands were inherently mild ones in obese or elderly individuals, but the same findings would doubtless be much more frequent if examination could be made at the beginning of diabetes instead of in the final stages. The observations are important as evidence that anatomic lack of islands is not an invariable prerequisite to the existence of diabetes, and as confirmation of other evidence of a functional deficiency. (c) Weichselbaum's so-called "atrophy" of islands is at least strongly suggestive of diabetes, but whether it is absolutely diagnostic remains uncertain. (d) Pancreatitis. There is no practical usefulness in trying to draw exact lines between the usual forms of inflammatory and degenerative lesions. One of the most suggestive indications of diabetes is fibrosis or hyalin limited almost specifically to the islands, but it is by no means infallible. Any intralobular inflammation may serve to arouse suspicion, but simple interlobular fibrosis or adipose invasion may be accompanied by diabetes. Careful search is desirable for even the slightest changes, which may have high importance as vestiges of past inflammation or accompaniments of serious functional derangements. On account of the latter element the microscopic diagnosis of diabetes can never be infallible throughout any long series by present methods, but the experience indicates that with an adequate number of fresh sections the great majority of cases coming to autopsy can be thus diagnosed. Examinations in the past have often not been sufficiently thorough, and to date there is no proof that a strictly normal pancreas is ever found with diabetes.

549 NON-DIABETIC CASES.

150 CASES OF ACUTE INFECTIOUS DISEASE.

These will be arranged in precedence according to the number of cases of each kind.

PNEUMONIA.

Pneumonia comprised 71 cases, of which 40 were lobar and 31 lobular. The deaths were at various stages, and various complications were present.

Of the 40 cases of lobar pneumonia (in one of which the Friedlander bacillus was mentioned as the cause) the pancreas was found normal in 20, or exactly half. Of the other 20 cases, a few small focal necroses were present in 1, and a slight fibrosis involved a few islands in 1. Fat was mingled with the fibrous tissue once, and predominated in a second case. Otherwise the changes were limited to a slight interlobular or patchy fibrosis. In 1 instance there was an apparently recent round-cell invasion with little fibrous formation; otherwise the changes appeared old. Extensive acute inflammations, such as described by Whipple, were not encountered. The abundance and normal appearance of islands excluded diabetes safely in all but 3 cases, where the diagnosis "diabetes possible but improbable" was made necessary by postmortem changes somewhat imitating vacuolation.

Of the 31 cases of lobular or bronchopneumonia, the pancreas was found normal in 17. In one of these the streptococcus was mentioned as the etiologic agent. In another, besides organizing pneumonia, chronic bronchitis, bronchiectasis and emphysema, mention was made of amyloid degeneration in the spleen, liver, kidneys, adrenals and bronchial lymph-nodes. Among the 14 cases of positive findings in the pancreas, these in 2 instances consisted only in edema of the connective tissue. In another case the pancreas was invaded by masses of mononuclear cells of undetermined type, widely separating the involuting acini, while the islands stood out intact; an "obscure infection" was mentioned in the autopsy report. In another case "embolic nephritis" was mentioned, and a similar process evidently took place in the pancreas, as indicated by small circumscribed patches of fibrosis. In 1 case there were small hemorrhages in both islands and acinar tissue, in another in the islands only. In 1 instance there was a sprinkling of adipose tissue without fibrosis. In 2 cases there was interacinar pancreatitis, slight in degree and without fibrosis of islands. In the other cases the fibrosis did not invade the lobules. The changes appeared recent in no more than 3 or 4 cases altogether; in all the others they seemed probably to antedate the pneumonia. There was nothing suggestive of diabetes in any case.

SEPTICEMIA

The next most numerous group consists of 28 cases characterized by septicemia. The classification was necessarily arbitrary, and the

line of separation indefinite from surgical cases, when the source of infection was a small focus such as a middle ear abscess, from endocarditis when the origin was there, and from pneumonia when the general seemed to predominate over the pulmonary infection. Peritonitis and abscesses of metastatic origin throughout the body were numerous in the list. The various strains of streptococci were the leading organisms, staphylococci next, and pneumococci third (including 2 cases of pneumococcus peritonitis).

The entire group may be divided into 20 cases in which peritonitis was absent, and 8 in which it was present. In the former series, the pancreas was found normal in 14 cases and altered in only 6. The cases with normal pancreas included 1 with embolic gangrene of both legs, and another with amyloid degeneration in liver, spleen, kidneys and adrenals. The 6 cases showing changes included 1 of small focal necroses, 2 of diffuse fibrosis (1 recent, as judged by round-cell invasion), and 3 of slight interacinar fibrosis. There was no fibrosis or degeneration of islands.

The 8 cases with peritonitis showed a widely different proportion of pancreatic changes, for the pancreas was normal in only 2 of them. 1 case of pancreatitis was a rather advanced old sclerosis, but the islands were intact. 2 cases were in the stage of round-cell invasion, but in them and also in all the others the islands were not appreciably damaged.

REMARKS.

A point of interest was the apparent immunity of the pancreas and especially its islands in a group of cases characterized preeminently by septicemia, metastatic infections, intoxications and all forms of injury by pyogenic cocci and other organisms. In some cases the most widespread petechial hemorrhages were reported throughout the body, but no hemorrhages were found in the pancreas. It is improbable, therefore, that hemorrhages sometimes found in the islands are of toxic origin. The peritonitis cases showed a much higher incidence of pancreatitis than in the surgical series, but it seemed to be seldom due to the immediate infection. There were no indications of diabetes or lesions likely to give rise to diabetes in the entire group.

TYPHOID.

Of 18 cases of typhoid fever, the pancreas was found normal in 9. Among the 9 pancreatic changes were 1 of small focal necroses, 2 of slight fibro-fatty invasion, 1 of slight diffuse fibrosis, and 4 of slight interlobular fibrosis. The islands appeared normal in all of these.

The remaining 1 case was remarkable, in that the pancreatic parenchyma was extensively replaced by adipose tissue; islands were still numerous, but a large proportion of them showed hyalin degeneration. As there was no hydropic change, the diagnosis was written, "diabetes probable but not certain". The possibilities open are that the hyalin in the islands antedated the typhoid infection or was caused by the

latter. A negative history does not necessarily exclude mild diabetes; also negative urinalyses in a cachectic typhoid patient are not decisive. If the hyalin islands were old, the patient may be considered certainly to have had either diabetes or a lowering of tolerance bordering on it. If the hyalin arose from the typhoid infection, diabetes would have been probable sooner or later after recovery, and the typhoid would then have been the cause of the diabetes, even though the first symptoms may have developed years afterward. Pancreatic studies in the past have been confused by according an unwarranted authority to clinical diagnosis. Hyalin or other destruction of a large proportion of the islands of Langerhans is proof positive of diabetes or a marked tendency in that direction. The lack of clinical demonstration in patients dying under various circumstances does not alter this essential fact.

12 CASES OF MENINGITIS.

3 of these were cases of acute cerebrospinal meningitis. 2 were in children, with normal pancreas. 1 was in a "large fat man" of 36 years, with slight fibro-fatty infiltration of the pancreas, and normal islands.

The other 9 cases were streptococcus, staphylococcus and 1 pneumococcus, having their origin from sinus infections or distant foci. The pancreas appeared normal in 5. 3 of the others were examples of slight fibrous or fibro-fatty patches. 1 was a case of diffuse fibrosis, slight in degree but apparently recent or progressive as judged by round-cells or young fibrous tissue. A few islands were invaded. There was no indication of diabetes at this stage, but the process was of a sort which might lead to diabetes if it should continue.

7 CASES OF POLIOMYELITIS.

All these cases were acute epidemic poliomyelitis in children ranging in age from 14 months to 5½ years. The pancreas appeared normal in 6. In the remaining 1 there was slight fibrosis involving chiefly the islands, though enough normal islands remained to exclude any probability of diabetes.

One question of interest in the above 19 cases involving the central nervous system was whether the nervous damage or irritation would be associated with vacuolation of islands or any other signs of diabetes. The findings as stated were negative from this standpoint.

4 CASES OF PLEURISY.

Of 4 cases of pleurisy or empyema, the pancreas appeared normal in 3, though in 1 of these there was a record of suppurative portal phlebitis, and in another of amyloid degeneration in liver, spleen and kidneys. In the 4th case the pancreatitis was rather extensive, both as interlobular bands and diffuse invasion, and active as indicated by round-cells accompanying the fibrosis. There was no direct involvement of islands and no evidence of diabetes.

10 CASES OF MISCELLANEOUS INFECTIONS.

These included the following:

- 2 cases of diphtheria, with normal pancreas.
- 1 case of acute enteritis, with slight fibrosis not involving islands; also
- 1 case of enteritis with thrush, with normal pancreas.
- 1 case of double pyonephrosis and nephrolithiasis, and terminal bronchopneumonia, with slight fibro-fatty infiltration in the pancreas.
- 1 case of measles in a child of 5 years, with normal pancreas.
- 1 case of echinococcus of liver, with slight interlobular pancreatitis.
- 1 case of glanders, with lesions reported in skin, muscle, spleen, liver, lungs, brain and meninges. The pancreas was normal except for a few small patches of sclerosis.
- 1 case of Rocky Mountain spotted fever, with mention of characteristic vascular lesions in skin, testes and adnexa, and cloudy swelling of liver and kidneys. Pancreas normal.
- 1 case of Schistosomiasis Japonica, with reported interlobular cirrhosis of liver, chronic interstitial nephritis, chronic perityphlitis, and hemorrhages into gastrointestinal tract. Normal pancreas.

39 SURGICAL CASES.

The principal conditions represented were the various common forms of sepsis, especially peritonitis from perforations of gastric and intestinal ulcers, gallstones, appendicitis, and gynecological conditions, with a few examples of infected limbs, sinus infections, strangulated hernia, and embolism of vessels. The named infecting agents included the streptococcus, staphylococcus, pneumococcus, and *B. proteus*. In 21 of these cases the pancreas was normal, and in 2 others it was normal except for a considerable infiltration with adipose tissue. In 16 cases distinct pancreatic changes were found as follows:

- 9 cases of slight fibrosis, with clinical diagnosis as follows:
acute appendicitis with abscess and acute diffuse peritonitis.
drainage of infected frontal and ethmoid sinuses, followed by acute suppurative meningitis, bronchopneumonia, septic infarcts and abscess.
- appendectomy, pneumonia and pulmonary abscess.
- hysterectomy, chronic endocarditis.
- appendectomy, general purulent peritonitis.
- duodenal ulcer; gastroenterostomy.
- induced abortion, gangrenous endometritis.
- appendicular abscess, pulmonary thrombosis.
- perforated gastric ulcer, generalized streptococcus peritonitis, lobular pneumonia, chronic nephritis.

In 4 of these cases fat was present as well as fibrous tissue. The changes were either interlobular or in scattered patches; the islands were not damaged or diminished, and there was no suspicion of diabetes.

- 1 case of an infant 17 days old, with perforated duodenal ulcer; bronchopneumonia and abscesses of lungs. The child was normally

delivered at full term, but had red eyes and snuffles from birth, and never thrived (syphilis?). In addition to fibrosis and frequent degeneration of the acinar tissue, the islands were fibrosed sometimes, but to such a slight extent as to raise no question of diabetes.

1 case diagnosed clinically as diaphragmatic hernia, with displacement and dilatation of stomach, edema of lungs and lobular pneumonia, acute fibrinous pleurisy, and fat necrosis. The pancreas contained scattered foci of acute hemorrhagic necrosis, but by far the greater portion of the parenchyma was uninjured and there was an abundance of normal islands.

1 case of cholelithiasis with stone impacted in ampulla of Vater; jaundice; hemorrhages in pleura, pelvis of kidney, and uterus; edema of lungs; fat necrosis. The pancreas showed slight recent inflammation and a few small focal necroses. Islands were numerous and normal.

There were the following 4 examples of diffuse pancreatitis, raising the question of diabetes:

1 case of acute gangrenous appendicitis with perforation, and chronic diffuse nephritis. There was slight intralobular pancreatitis; the acini often stained abnormally, and islands were scarce and small. It was impossible microscopically either to diagnose diabetes or to exclude it positively.

1 case of duodenal ulcer, with peritonitis following operation, and central necroses in the liver. The pancreas showed generalized invasion of fibrous tissue and round cells, and scarcity of islands. Autolytic changes prevented detailed study, and no judgment could be formed concerning diabetes.

1 case of cholelithiasis, death after cholecystectomy, with bronchopneumonia, abscesses and infarct of lungs, fibrinous pleurisy, syphilis of aorta, and fat necrosis. The pancreas showed thin fibrous bands spreading diffusely through the parenchyma, but a fair number of normal islands were present, rendering diabetes very improbable.

1 case of thigh amputation for gangrene of leg; arteriosclerosis, chronic pulmonary tuberculosis, and hyalin degeneration of vessels of the spleen. There was marked diffuse pancreatitis, but islands were so abundant and normal-appearing as practically to exclude diabetes.

REMARKS.

The 39 surgical cases nearly all represented acute deaths from infectious accidents. Though 16 instances of pancreatitis were found among this number, in no more than 3 or 4 cases were the changes of a character to be attributed to the terminal illness. The cases may rather be interpreted as typifying a similar proportion of chronic pancreatitis among the population at large, or at least among the ailing portion of the population. Furthermore, they indicate that the most extreme local or systemic infections and accompanying intoxications generally produce no extensive changes in the pancreas. This holds even for infections closely bordering upon the pancreas, such as peritonitis. The few cases with acute pancreatic inflammation or necrosis all had clear local causes, such as an obstructing gallstone, diaphrag-

matic hernia, etc. On the other hand there were 2 cases of cholelithiasis (with operation) among the negative series. There was no basis for a diagnosis of diabetes in any instance, but it was impossible to exclude it positively in all of the 4 cases of diffuse pancreatitis.

39 CASES OF TUBERCULOSIS.

The various forms, of pulmonary, bone, glandular tuberculosis, etc. were represented, with and without complications. As the tuberculosis was evidently the cause of death in all but 1 instance, several organs were generally involved.

There were 28 cases with normal pancreas, and 1 other in which there was nothing more than a slight sprinkling of fat tissue. Of this number, 14 were described as cases of generalized miliary tuberculosis. In 1 case, amyloid degeneration of retroperitoneal and cervical lymph-glands was mentioned.

Pancreatic abnormalities were found in 10 cases, of which 6 were generalized miliary tuberculosis. In 2 of these 6, there were a few miliary tubercles as the only lesion in the pancreas, and in 1, a slight general fibrosis in addition. The other 7 cases (3 miliary, 4 non-miliary) showed merely slight to moderate fibrous or (in 1 case) fibro-fatty infiltration. In 4 of these instances the fibrosis was interlobular or patchy, not involving the islands. In the remaining 3 instances the fibrosis was diffuse and involved the islands, but to such slight degree as to raise no serious question of diabetes. In 1 case there was mention of hyalin degeneration of follicles in the spleen, and in another of amyloid degeneration in the spleen, liver, adrenals, kidneys and mesenteric lymph-nodes; but corresponding changes were not found in the pancreas.

In general, the features of chief interest were the absence of hyalin degeneration and of changes suggesting diabetes, and the lack of indications of any special injury of the islands by the toxins of tuberculosis.

9 CASES OF BRAIN ABNORMALITIES.

For evident reasons, separate classification is made of abnormalities involving the brain. 5 of these were traumatic, as follows:

1 fracture of skull, 1 cerebral hemorrhage with death 10 days after trauma,
1 bullet wound of brain, 1 acute encephalitis inferior with history of heavy hammer blow on head 17 months before. Normal pancreas in all. 1 case of fracture of base of skull, death having followed within a few hours after an automobile accident. Fibrosis in the pancreas was very slight, but considerable areas of the parenchyma were replaced by adipose tissue.

The non-traumatic cases were 1 of amaurotic familial idiocy, 1 of atrophy of left cerebral hemisphere and cyst of cortex, 1 of pachymeningitis interna hemorrhagica, and 1 of bilateral progressive degeneration of lenticular nuclei, all with normal pancreas except for a few island hemorrhages in the last.

11 INTOXICATION CASES.

These included the following:

- 5 cases of gastrointestinal intoxication in young children, with normal pancreas.
- 4 cases of acute bichloride of mercury poisoning, the pancreas being normal in 1 and the fibrous tissue slightly increased in 2 others. In the remaining cases the pancreas showed marked fibro-fatty changes and round-cell invasion; islands were scarce in the single slide available, but no fibrous, degenerative or other changes were observable in those found.
- 1 case of chronic lead poisoning, with arteriosclerosis and nephritis. Normal pancreas.
- 1 case of acute and chronic alcoholism, with psychosis and peripheral neuritis. There was a slight diffuse fibrosis, with no perceptible injury of islands at this stage.

70 CASES OF NEOPLASM.

In 27 of these cases the pancreas appeared normal. This list included the usual forms of malignant tumors of various parts of the body. There was extensive involvement (by the primary growth or metastases) of the gastrointestinal tract in 7 cases, of the liver in 6 cases, of the brain in 4 cases, while general carcinomatosis was mentioned in 1 case. The apparent immunity of the pancreas to either direct or indirect injury seems all the more remarkable under these circumstances.

There were 17 cases of direct invasion of the pancreas by tumors. In 5 of these the great mass of pancreatic tissue, apart from a narrow zone bordering the tumor, appeared normal. There were 3 sarcomas and 2 carcinomas in this list. Also some of the above cases represented massive involvement of some part of the pancreas in a large growth, and others a scattering of small metastatic nodules throughout the gland. In 12 cases (3 sarcoma, 9 carcinoma) the sections of pancreas containing no tumor still showed more or less fibrosis. In 1 of these cases adipose infiltration was marked. Near the advancing margins of the tumors, the islands were always better preserved than the acini, which generally were in various stages of involution. In general islands were abundant, free from fibrosis, and apparently normal, except in the following instances. In 1 case a dozen pancreatic sections were available. The head of the gland was completely destroyed by a carcinoma originating from the gall-bladder. The rest of the gland (presumably from stasis of secretion) showed very extensive fibrosis, but a sufficient number of intact islands remained to exclude diabetes with fair probability. In 2 cases, pancreatitis was slight but islands were noticeably scarce and small. Those found were free from fibrosis or other abnormalities, and diabetes was therefore considered improbable. 1 other case was similar, except for fibrosis in some islands. No vacuolation was seen, but the combined scarcity and fibrosis of islands was made the basis of a diagnosis of diabetes. The clinical

diagnosis contradicted this assumption, which was hazardous on such a basis. It is impossible to be certain whether the microscopic judgment was entirely erroneous, as it might well have been when based on only 1 slide, or whether the pancreatic damage actually sufficed for diabetes but the latter was prevented by cachexia. On the other hand, the diagnosis of diabetes was altogether missed microscopically in 1 case in which it was reported clinically present. This case (No. 8750) was included in the series of 21 diabetic cases.

In 26 other cases pancreatitis was found, though there was no tumor invasion of the gland. In 1 of these cases the tumor was a hypernephroma originating from the right adrenal. The fibrosis in all these cases was slight and spared the islands, so that there was no suspicion of diabetes.

48 CASES OF LIVER DISEASE AND GALLSTONES *

1 case bore the diagnosis of cholelithiasis, with calculi in cystic duct, chronic cholangitis, fatty degeneration of liver, nephrolithiasis and chronic pyelitis. There was slight interlobular pancreatitis, in an active stage as indicated by numerous round-cells and fibroblasts. Islands were not numerous but were apparently uninjured.

1 case was hypertrophic cirrhosis, with normal pancreas.

17 cases were atrophic cirrhosis in various stages, mostly extreme. In 1 case the pancreas was normal, or fibrosis was at least questionable. In the other 16 cases, there was interlobular pancreatitis. In 1 of these cases the fibrosis was trivial, but there was a considerable sprinkling of fat cells. In 11 other cases the fibrosis was slight, though in 1 of these there was slight fibrosis of islands in addition. In 4 cases the pancreatitis was of marked degree, and in 3 of them there was diffuse fibrosis in addition to the interlobular bands, and the islands were involved. The destruction of islands was never sufficient to warrant a diagnosis of diabetes, but diabetes could not be excluded in any of these 3 cases. Even after disclosure of the clinical diagnosis, it remains an open question whether the patients might have been diabetic if they have been brought to a normal nutritive state in other respects. It may be noted that neither the toxins of cirrhosis nor the frequent ascites produced hydropic changes in the islands.

* Reference was made elsewhere (Rockefeller Institute Monograph No. II, p. 633) to the work of Halsted, Opie, Flexner and others regarding gallstones, bile and duct infections as causes of pancreatitis. Heiberg (*Krankheiten d. Pankreas*, pp. 195-197) considers jaundice rare among the symptoms of pancreatitis. He also finds diabetes rare with gallstones, supposedly because pancreatitis resulting from them is interlobular. Joslin (*Treatment of Diabetes*, 1917, p. 295) tabulates 20 cases of diabetes following gallstones in his experience. Mitchell (*Medical Record*, Oct. 1, 1921) reported 116 diabetic cases from the Physiatrie Institute, which had been specially studied with reference to the etiology. In his Table 2, showing 8 cases in which infection was an immediate antecedent of diabetes, 4 of these cases were of icterus or cholecystitis. In his Table 3, showing 43 cases of suggestive relationship between diabetes and some prior pathologic condition, 10 of the cases were of liver or gall-bladder trouble.

The close relations of the liver and pancreas lend interest to the question how

In addition to the above cases in which the conditions were mentioned as the direct or principal cause of death, incidental mention of cirrhosis or gallstones was made in 29 cases here classified under various other diseases.

Of 13 cases in which cirrhosis of the liver was incidentally mentioned, the pancreas was found normal in 7. In 1 of the remaining 6, the pancreatic changes were merely those attending the direct invasion of a carcinoma. In the other 5 cases, slight fibrosis was present, interlobular in 3 cases and diffuse in 2 cases, but in only 1 of the latter were islands fibrosed, and here not to a degree suggesting diabetes.

Of 16 cases in which incidental mention was made of gallstones, the pancreas was found normal in 6. In 3 others, there was merely more or less fatty replacement of parenchyma. In 5 others there was only slight interlobular or patchy fibrosis, not involving islands. In 2 cases there was marked diffuse fibrosis, with no primary involvement of the islands; in 1 of these the islands appeared normal, while in the other they were scarce and the swallowing up of whole lobules in fibrosis must have involved destruction of numerous islands.

It may be noticed in addition that cholelithiasis was present in 3 of the 21 diabetic cases described at the outset.

22 CASES OF METABOLIC DISORDERS.

Of 2 cases of exophthalmic goitre, there was found slight fibro-fatty change in one and a normal pancreas in the other.

In 1 case of gout, described as having extensive urate deposits and arteriosclerotic contracted kidneys, the pancreas was normal.

In 1 case of Addison's disease, the pancreas was normal.

In 1 case of pellagra the pancreas was normal.

In 1 case of multiple neuritis, there was very slight pancreatitis, including slight fibrosis in a few islands.

Of 2 cases of status lymphaticus in adults, there was found a normal pancreas in one, and in the other a slight diffuse pancreatitis, with fibrosis and distortion of some islands, though the majority remained normal.

Of 6 cases of rickets, the pancreas appeared normal in 4. Of the 2 cases with slight interlobular fibrosis, 1 was a Negro baby of 9 months with giant-cell pneumonia, and the other a 3½ year white child with chronic lymphadenitis and pulmonary osteo-arthritis.

Of 8 cases of infantile marasmus or malnutrition, the pancreas appeared normal in 6. 1 other was normal except for occasional hemorrhages into islands. In the remaining one there was slight diffuse pancreatitis, including slight fibrosis of some islands.

often they are simultaneously diseased. It is evident that though the coincidence is frequent, either organ is sometimes sclerosed while the other is normal. Heiberg (p. 183) quotes Weichselbaum's view that alcoholism may cause interlobular pancreatitis even without hepatic cirrhosis, and Lissauer's finding of a normal pancreas in only 7 out of 24 alcoholics.

22 CASES OF BLOOD AND GLANDULAR DISEASES.

Of 8 cases of pernicious anemia, there were found 5 with normal pancreas, and 3 with slight pancreatitis not involving the islands. In 1 of the latter there were occasional hemorrhages in the islands.

Of 3 cases of myeloid leukemia, slight pancreatitis was found in 1 and normal pancreas in 2.

Of 2 cases of lymphatic leukemia, normal pancreas was found in 1 and slight patchy fibrosis in the other.

2 cases of Hodgkin's disease showed normal pancreas.

1 case of Banti's disease, and 1 of great splenic enlargement of undetermined character, showed slight interlobular pancreatitis.

2 cases of extreme secondary anemia with hemorrhages into various organs showed normal pancreas.

Of 3 cases of purpura or interstitial hemorrhages of unknown origin, 2 showed slight interlobular pancreatitis without involvement of islands. The third was an 11-day infant, with a more marked degree of the same, the fibrous tissue appearing so firm and well organized as to suggest an intrauterine origin of the change, though the condition was not recorded as syphilitic.

53 CASES OF HEART DISEASE.

The pancreas was found normal in 20 cases, including 16 chronic and 4 acute. Endo-, myo- and pericarditis were represented, with the usual list of complications. A rheumatic origin was mentioned in a number of instances, but generally the etiology was not stated.

Fibrous changes were found in the pancreas in 25 cases, and fibrofatty in 8 cases. 1 case was acute endocarditis, the other 32 were various chronic cardiac disorders. The pancreatitis was slight in all cases, and in all but a few cases consisted in an interlobular or patchy infiltration of fully formed fibrous tissue. In 1 case of chronic and acute endocarditis, arteriosclerosis, anasarca, and acute enteritis and colitis, there was diffuse invasion of the pancreatic parenchyma with round cells and young fibrous tissue, but the islands remained intact. There were hemorrhages into islands in 2 cases. Fibrosis of islands was encountered only once in the entire series, and here it was so slight and infrequent as to raise no question of diabetes. Diabetes required consideration in 5 instances, on account of postmortem changes. In 2 cases these slightly imitated vacuolation, and in 3 cases they prevented study of the cytology in slides where islands were rather scarce. Diabetes could therefore not be excluded positively, though it was rated as improbable.

There were 3 points of special interest in connection with the cardiac series. First, with the supposed occasional circulation of pathogenic organisms in the blood, there was the possible question of pancreatic damage. In fact, the proportion of 33 cases of pancreatitis out of a total of 53 was high; but the changes were mostly slight, and in view of the almost complete immunity of the islands, it is questionable whether they were due to organisms or toxins derived from the blood.

Second, the influence of chronic passive congestion may be considered. Theoretically, this also should affect the islands, and it may at least be concluded that no injury of them from this cause is demonstrable. Third, with extensive general or local edemas, particularly ascites, it might be imagined that hydropic changes in the islands might be produced or imitated, but none such were found. On the whole, the healthy state of the islands in this series corresponds to the clinical experience that there is no special concurrence of cardiac disease and diabetes.

75 CASES OF NEPHRITIS.

Of 8 cases of acute nephritis, the pancreas was found normal in 5. 1 case showed slight interlobular fibrosis, another fibro-fatty invasion and one small fat necrosis, and another slight diffuse pancreatitis. The islands remained apparently normal in all the cases.

In 3 cases classified as subacute and chronic nephritis, the pancreas was normal.

No classification will be attempted among the 64 cases of chronic nephritis, but the great majority were recorded as interstitial, diffuse or arteriosclerotic in type. The pancreas was found normal in 34 cases. In one of these the patient had died from hemorrhage into the lateral ventricles before reaching the ward. His complaint had been of "diabetes and nervousness", but the urine contained no sugar. Islands were noticeably scarce, but the advanced autolysis prevented accurate study. The apparent absence of pancreatitis was one point against diabetes. Of the 30 cases with pancreatic changes, in 21 there was found merely fibrosis of trivial degree and apparently long standing. In 4 cases fatty replacement of parenchyma was much more prominent than fibrosis. In 1 case with considerable old fibrosis there were a few foci of recent necrosis; these were mentioned in the autopsy report as being similar to the process in the kidney in the same case. In 3 cases with marked diffuse fibrosis and more or less arteriosclerosis in the pancreas, the question of diabetes was raised but answered negatively because of the relatively uninjured state of the islands. In 1 case there was diffuse pancreatitis in the form of light strands of fibrous tissue and many round cells and fibroblasts; islands were scarce though no active destruction was apparent. 1 island was found showing questionable vacuolation in 2 cells, which was regarded as probably significant, inasmuch as the autopsy was only 2 hours after death. Accordingly a microscopic diagnosis of diabetes was hazarded. According to the clinical record this was a mistake, and it might have been avoided if more sections had been available, which might have disproved the supposed scarcity and vacuolation of islands. On the other hand there is the bare possibility of the existence of diabetes with absence of glycosuria owing to impermeable kidneys.

102 CASES OF ARTERIOSCLEROSIS.

In 20 cases arteriosclerosis was the chief feature of the autopsy, when the deaths had occurred from apoplexy, coronary obstruction or senile accidents. In 9 of these cases the pancreas appeared normal, and not even sclerosis of the vessels was noticeable. The ages of these patients ranged from 35 to 88 years. It is noteworthy that some of the oldest individuals and some of the most marked examples of general arteriosclerosis in the entire series were included among this group with normal pancreas. In 7 cases there was no true pancreatitis, but the vessels were more or less sclerosed and there was considerable fatty replacement of the parenchyma. In 4 cases there was widespread fibrosis, interlobular or patchy in distribution, with very little involvement of islands. In 1 of these cases islands were scarce in the slide examined, and diabetes could neither be diagnosed nor excluded.

Additional mention may be made of 82 cases classified under other diseases, in which the autopsy report mentioned extensive arteriosclerosis. 10 of these were diabetic cases, with abnormalities in the pancreas. Of the other 72, the pancreas was normal in 35. In 28 there was merely slight fibrosis. In 2 the fibrosis was more marked and diffuse and involved some islands. In 7 the change consisted in fatty replacement with or without slight fibrosis.

28 CASES OF SYPHILIS.

There were 16 cases in which syphilis was the chief diagnosis. 3 of these were infants with typical extensive lesions. In the 13 adults, death resulted from involvement of the vascular or nervous system. There were 6 cases in which the pancreas appeared normal. 1 of these was a 7-½ months infant with congenital syphilis involving the lungs, bones, and testes, also with hyalin necrosis in spleen follicles, but the absence of pancreatic changes observed by the writer was corroborated in the autopsy report. 10 cases showed pancreatic changes. 8 of these were adults. In 5 of these the changes were slight, limited to interlobular thickening and small patches of fibrous and cellular invasion. In 3 the inflammation was marked and diffuse, but in only 1 of these were the islands appreciably involved, and here not to a degree suggesting diabetes. Of the 2 congenital cases, there was a very slight patchy infiltration of the pancreas in an infant of 6 weeks dying of subdural hemorrhage with syphilis of the liver and bones. The other died of malnutrition and bronchopneumonia at 3 months, with syphilitic changes in the myocardium, bones and pancreas. The latter consisted of a severe grade of fibrous and round-cell invasion, spreading diffusely and strangulating the parenchyma. The few islands found were surrounded but not actually invaded by the fibrosis. There was no vacuolation, and diabetes was suggested as possible but not probable.

There were also 12 cases recorded under other diseases, where syphilis was mentioned in the autopsy report, chiefly as a cause of aortitis. In 7 of these the pancreas appeared normal. In 5 there was

slight to moderate pancreatitis, involving the islands only slightly in 1 case.

4 CASES OF PANCREATIC DISEASE.

4 cases with marked pancreatic changes were picked out for special discussion in relation to diabetes.

1 case was described as periarteritis nodosa in a child of 10 years, involving most of the organs, and with exquisite lesions in the pancreas. The islands, though sometimes distorted, remained evidently sufficient in size and number, and were free from vacuolation or "atrophy". Diabetes was therefore excluded in this case.

Another patient was an 11-day infant, with cerebral hemorrhage, hemorrhagic infiltration of tissues of scrotum and of right foot, and diffuse cirrhosis of pancreas. There was very extensive intralobular fibrosis and round-cell invasion of the entire parenchyma, including islands. The islands nevertheless seemed approximately normal in number, and no positive vacuolation could be found. Such a process if continued must almost inevitably give rise to diabetes, but it is not possible to estimate at just what stage systems will begin. Diabetes was therefore mentioned as possible, with no attempt at a positive decision.

Another case (age 44 years) bore the diagnosis of infection, hemorrhage and extreme fibrosis of the pancreas, acute sero-fibrinous peritonitis, chronic pleurisy, early bronchopneumonia, perihepatitis, and focal necroses in the liver. Glycosuria was absent as determined in 9 tests at intervals. The fibrosis of the pancreas was very advanced, but mostly interlobular; numerous islands remained and were free from fibrosis, vacuolation or "atrophy". On this basis the diagnosis was written, "Probably no diabetes, though mild form is possible".

The fourth patient was 63 years of age, was in the hospital 10 days without glycosuria, and bore the diagnosis of acute diffuse peritonitis, cardiac hypertrophy and dilatation, hydrothorax, and chronic passive congestion of viscera. On gross examination it was noted that the pancreas was large and stony hard, and there was no fat necrosis. Microscopically there was a severe grade of acute diffuse pancreatitis, with fibrin, polymorphonuclear leukocytes, round cells and fibroblasts penetrating everywhere between the acini. Islands were fairly numerous and were almost completely spared, but there were doubtful appearances of slight vacuolation in a few of their cells. On this basis the diagnosis of diabetes was hazarded. Evidently the impression of hydropic degeneration was mistaken, for its occurrence is improbable except with severe active diabetes. Except for this mistake, the sparing of the islands might have been interpreted to exclude diabetes even with an inflammation of this severity. This does not imply that this character of inflammation may not be diabetogenic, for its further advance might well have produced injury of the islands.

20 CASES OF OBESITY.

No cases are classified under this heading alone; but of those already listed under various causes of death, there were 20 in which the autopsy records made mention of great obesity. Of these 20 cases, the pancreas was found normal in 7. 4 of these 7 patients were about 50 years old; 1 was 64 years, 1 was 39, and 1 was 29 years. Cirrhosis, fatty liver and arteriosclerosis were frequent in this list, and 1 patient had gout. Of the 16 cases with pancreatic changes, the greater number were above 50 years, but there were individuals aged 39, 35, 31, 25 and 18 years respectively. The associated conditions were similar to those already mentioned. The pancreatic changes consisted in 7 instances in arteriosclerosis and slight fibrosis, mostly interlobular, but in 1 instance the fibrosis was intralobular and in 1 other there was distinct fibrosis of islands, but not to a degree indicative of diabetes. In 6 other cases the pancreas contained more or less extensive areas of adipose tissue, but this was always accompanied by some degree of fibrosis. The occurrence of fat in the pancreas was not determined by the degree of obesity; some of the patients with most extreme obesity, in whom the pancreas was described as embedded in fat, had strictly normal pancreas, and others showed simple fibrosis.

For comparison, search of the entire non-diabetic series of cases revealed 10 in which the pancreas contained appreciable amounts of adipose tissue, without obesity or even in the majority of instances with decided emaciation.

THE PANCREAS AT DIFFERENT AGES.

The following cases in which the ages were ascertained were classified for a statistical record of pancreatic pathology according to periods of life. All abnormalities were lumped under the general head of "pancreatitis".

PERIOD OF LIFE	No. of Cases	Normal Pancreas		Pancreatitis	
		No.	%	No.	%
Below 1 year.....	37	27	73	10	27
Remainder of 1st. Decade (1 to 9 years).....	42	34	81	8	19
2nd Decade.....	34	20	60	14	40
3rd Decade.....	54	39	72	15	28
4th Decade.....	79	37	47	42	53
5th Decade.....	101	47	43	62	57
6th Decade.....	99	32	35	59	65
7th Decade.....	61	21	34	40	66
8th Decade.....	14	5	36	9	64
9th Decade.....	3	1	33	2	67

Average for Average for
6 later dec- first 8 dec-
ades, 62% ades 28.5 %

DISCUSSION OF NON-DIABETIC CASES.

1. *Percentage of pancreatic abnormalities.*—Of the total number of 549 non-diabetic cases, the pancreas was found normal in 285, or 52%, and pathologically altered in 264, or 48%.

2. *Types.*—The various types of changes were mentioned under the different series of cases. Recent, acute or subacute lesions were the least common. There were 10 cases with focal necroses, and 12 with active round-cell invasion. Separate mention may be made of 2 cases with tubercles, 1 with periarteritis nodosa, and 17 with tumor invasion of the pancreas. Hemorrhages into the islands were observed in 6 cases, but without any uniform or discoverable cause or meaning. Adipose replacement of areas of parenchyma was more frequent, generally in association with fibrosis or arteriosclerosis, not in any strict relation with obesity, though more common in obese patients. By far the preponderant change was some degree of sclerosis, generally slight. Interlobular fibrosis was the commonest, but intralobular forms were also represented, including some fibrosis of islands.

3. *Accompanying conditions.*—Cirrhosis of the liver, when of a degree sufficient to cause death, was accompanied by pancreatitis in 16 out of 17 cases. Pancreatitis was also present in a majority of cases of gallstones, arteriosclerosis, syphilis, and obesity. It is equally important to mention that it is possible for the pancreas to be absolutely normal in all of these conditions, as far as the present observations could decide. Age is indicated as a very important factor; the general average of pancreatic abnormalities in the first 3 decades of life was 28.5%, in the subsequent 6 decades 62%.

4. *Hydropic degeneration.*—Mention was made in the text of a few instances in which the diagnosis was confused by postmortem changes somewhat resembling vacuolation of island cells. Others not mentioned brought the total up to 24 cases in which it was impossible to exclude hydropic degeneration and with it the possibility of diabetes. The difficulties thus created are serious, because, especially with more or less pancreatitis present, the decision between severe diabetes and entire absence of diabetes may hang upon such a doubtful interpretation. No such difficulties exist with thoroughly

fresh material, or with the degree of freshness represented in the great majority of specimens in this series. The principal lesson from the study is that true hydropic degeneration does not occur outside of diabetes.

Microscopic diagnosis of diabetes.—In addition to the list of doubtful appearances of hydropic degeneration due to postmortem changes, there were 10 in which more or less suspicion of diabetes was created by the character of the pancreatitis present and the apparent scarcity of islands. A greater number of sections would have permitted better judgment, but pathological examination can scarcely be expected to gauge the exact degree of pancreatic damage, especially in view of the known wide discrepancies between structure and function in all other organs. On the other hand clinical records are seldom conclusive, and the mere absence of glycosuria under conditions of illness and cachexia by no means establishes the absence of diabetes, or especially of a pathologically lowered carbohydrate tolerance.

SUMMARY AND CONCLUSIONS.

1. *Total statistics.*—Pancreas specimens were studied in a total of 570 cases. Abnormalities were found in 48% of the 549 cases which were clinically non-diabetic, and in all of the 21 cases which were clinically diabetic.

2. *Incidence and etiology.*—Significantly high proportions of pancreatic lesions were found in association with cirrhosis of the liver, gallstones and syphilis, indicating probable etiologic relationships. A high proportion also occurred with arteriosclerosis, whether because the same agency produced the vascular and pancreatic alterations, or the changes in the vessels caused those in the pancreas, or perhaps to some extent because arteriosclerosis is commonest in the elderly. The proportion of pancreatic changes was also high with obesity, affording an anatomic basis for the frequent association with diabetes, in addition to the functional burden imposed by obesity. There were 10 cases with focal necroses and 12 with active round-cell invasion, mostly in connection with acute or subacute infections; very few of these were extensive enough to create any apparent danger of diabetes, but were interesting for general indications of the causes of pancreatic injury. Age

appeared as a very important factor; in the non-diabetic series pancreatic abnormalities were found in 28.5% of cases in the first 3 decades, and in 62% of cases after that time. The great majority of diabetic cases in this series, just as of diabetic cases everywhere, occurred after the third decade. The figures permit a fairly clear interpretation that the pancreas is subject to various infectious and toxic injuries from infancy onward, the results being cumulative with years and also the tendency to injury being greater in later life. Most of the injuries are trivial in degree and never cause perceptible symptoms, but occasional more severe injuries damage the islands in structure or function so as to give rise to diabetes either immediately or many months or years later. These statistics agree with those of Whipple and others in indicating that the pancreas is an organ which is very frequently diseased, even when localizing symptoms are entirely absent. Not only is the etiology of diabetes thus freed from mystery, but it is testimony to the recuperative power of the pancreas that many more persons do not become diabetic. At the same time two contrary facts deserve mention. First, these statistics are from hospital patients with fatal diseases, therefore it is not to be supposed that an equally high proportion of pancreatic lesions will be found among the general population at corresponding ages. Second, the observations indicate that the pancreas may be entirely normal even with hepatic cirrhosis, gallstones, syphilis and every other kind of acute and chronic infection, obesity, or senility.

3. *General pancreatic pathology.*—A. Non-diabetogenic lesions.

(a) *Focal necroses* are one of the common forms of injury with infections or intoxications, but generally involve the acinar tissue and are not extensive enough to produce diabetes unless associated with functional damage.

(b) *Acute pancreatitis*, with hemorrhages or fat necroses, was rare in this series. The severe forms are known to be rare, and the accompanying prostration often prevents glycosuria. It may be localized, so that sloughing or removal of part of the gland may still leave enough sound tissue to prevent diabetes, or after a generalized inflammation there may be adequate repair, as demonstrated in animals.

(c) *Hemorrhages*, especially in the islands, are found oc-

asionally, with no fixed relation to other general or local disturbances, infections, intoxications, blood or vascular diseases or other known cause. It is even possible that they sometimes result from postmortem trauma, or are an agonal occurrence, especially as the extravasation is generally so fresh. As they occur both with and without diabetes, they may be classed as indifferent with regard to diabetes.

(d) *Adipose tissue* is not a normal element of the pancreatic parenchyma, but is not uncommonly found in routine autopsies. It is most frequent with obesity, but also is present without obesity and absent sometimes with extreme obesity. More or less fibrosis generally accompanies. The fat tissue apparently replaces parenchyma which has been lost either through inflammation or through impaired nutrition, as in arteriosclerosis.

(e) *Fibrosis* is the commonest change in the pancreas, and may apparently represent the vestiges of acute inflammations, or the consequences of chronic infections (syphilis), duct stasis, arteriosclerosis, etc. The commonest forms are interlobular or patchy, which are the least likely to cause diabetes. No absolute line can be drawn, however, regarding either the type or degree of fibrosis which may be associated with diabetes. Tumor invasions often give rise to fibrosis throughout the pancreas, but diabetes is rare, either because the islands are not sufficiently damaged, or because glycosuria is suppressed by cachexia. Hyalin degeneration, pigment deposit (hemochromatosis) and practically all forms of pancreatic destruction except hydropic degeneration are accompanied by fibrosis, and even when islands are involved an exact boundary cannot always be drawn between diabetes and its absence.

B. Diabetogenic Lesions.

(a) *Acute pancreatitis*. — Acute or subacute inflammation of the pancreas is known to be sometimes attended by glycosuria, but the typical findings in diabetic cases are not of this character. On the other hand, a few acute inflammations seen in this and also in Whipple's series appear to create damage sufficient to cause diabetes, and this possibility is corroborated by animal experiments. Also the changes found in diabetic cases often seem interpretable as the remains of former inflammatory injury. This sequence of observations

is the basis for assuming acute pancreatitis as an important cause of diabetes.

(b) *Adipose replacement* is perhaps never extensive enough to be of itself a cause of diabetes, but is worth noticing as an indication of pancreatic damage from inflammatory or degenerative causes, which sometimes is accompanied by diabetes.

(c) *Specific island lesions* are one of the most suggestive signs of diabetes. Fibrosis, alone or with hyalin degeneration, occurring in the islands with little or no involvement of the acinar tissue, is evidence of some circulating agent injuring the islands, and even when the visible changes are not great the functional damage may suffice for diabetes. Weichselbaum's "atrophy" is a specific change in the island cells, which is probably never found without some degree of fibrosis, and is probably interpretable as a sign of infectious or toxic injury or impaired nutrition. Its specificity to diabetes is not thoroughly established, especially as some islands may be thus altered while enough sound ones remain to prevent diabetes; but it is probable that fully "atrophic" islands are incapable of function, and this picture in a high proportion of the islands is a strong indication of diabetes.

(d) *General fibrosis* of some grade is the commonest pancreatic change with diabetes. As pointed out by Opie, the diffuse or intralobular form which invades islands as well as acinar tissue, is the most characteristically diabetogenic, but this form may be present without diabetes, while on the contrary the interlobular form with no visible involvement of islands is sometimes associated with diabetes. This fibrosis may represent a chronic infection, such as syphilis, or the remains of single or recurrent acute inflammations. The question of progressiveness is hard to decide, since even an active process with cellular infiltration may recede instead of advancing; but it is worth pointing out that the lesions found in most diabetic cases appear more or less quiescent, the signs of progressiveness are no greater in young than in old patients, and are often entirely wanting in the severe youthful cases which are clinically the hardest to control. Furthermore the degree of fibrosis bears no absolute relation to the existence or severity of the diabetes; trivial fibrosis may be an indication of an intense previous inflammation which

has been largely repaired except for structural or functional injury of the islands sufficient to produce diabetes.

(e) *Scarcity of islands* may result from inflammatory or toxic destruction or from hydropic degeneration. Particularly from the latter cause, their size also is sometimes noticeably small. Minor reductions of this sort are often suggestive but necessarily difficult to judge. Perceptible reductions were present in the great majority of cases in this series. Extreme scarcity of islands is probably absolutely diagnostic of diabetes if found in numerous slides representing the different portions of the gland. Such scarcity is not necessary to the existence of diabetes, which may be present in a degree sufficient under bad management to cause death from acidosis or infectious accidents, when there is a noticeable abundance of large normal-appearing islands. This fact is one of the strongest proofs of functional deficiencies of the islands. On the other hand it is probable that all such cases under efficient treatment are genuinely mild and capable of a fairly high carbohydrate assimilation, and that the severest forms of diabetes with actually minimal tolerance occur only with marked anatomic deficiency of islands.

4. *Specific effects of diabetes.*—The one anatomic effect of diabetes upon the pancreas is hydropic degeneration, causing loss of cells and reduction of islands as previously stated, without inflammatory reaction or fibrous replacement. This actual destruction of island tissue by functional overstrain in the course of active diabetes furnishes the explanation of the irreparable lowering of assimilation which results, and is the strongest reason for thorough dietetic control. In most human cases only a minority of island cells are found vacuolated at one time, and this phenomenon is one proof of functional deficiency in the cells which still appear normal. Hydropic degeneration was positively identified in 3 cases of this diabetic series, and was evidently present in 5 others where it was blurred by postmortem changes. This vacuolation, being the result and the sign of intense functional exhaustion, as previously explained, goes with intense activity of the diabetic process. Thus it occurs in most coma cases even when the diabetes is inherently mild, and in any active severe diabetes, but not in mild diabetes nor in severe cases controlled by treatment. Postmortem changes not only blur true vacuo-

lation but sometimes partially imitate it. Mention was made in the non-diabetic series of a few instances of confusion from this cause, which are not encountered when the tissue is fully fresh. The chief lesson of the present series is that hydropic degeneration is never found except with diabetes. Therefore its presence, even in a single cell, is absolute proof of diabetes, but its absence is no proof of the absence of diabetes.

5. *Microscopic diagnosis of diabetes.*—The actual trial included 19 diabetic cases, in 5 of which diabetes was positively diagnosed and in 12 was recognized as possible. For an attempt based on study of a few routine sections, the record is satisfactory. In the great majority of the 549 non-diabetic cases, diabetes was easily and positively excluded. The question of diabetes was raised, or at least its exclusion was not positive, in 34 cases, i.e., a number greater than the entire diabetic series. In 24 of these cases the question was merely one of hydropic degeneration owing to postmortem changes. In fresh tissue the finding of genuine vacuolation, which is a sign of active diabetes, can scarcely stand in any conflict with the clinical record, except in uncommon cases of hyperglycemia with absence of glycosuria due to renal impermeability. In the other 10 cases the question of diagnosis depended upon the type of fibrosis, destruction of islands, etc. Though it is impossible to gauge the degree of island injury exactly, it is also wrong to accept the clinical record as infallible, since mild diabetes may give no subjective symptoms and glycosuria may be suppressed in an intercurrent illness. At least a lowering of carbohydrate tolerance must be indicated by any extensive pancreatic damage, and when this has been missed by the clinician, the clinical diagnosis is usually more subject to amendment than the pathological diagnosis. Under the best conditions, either the diabetogenic lesions or hydropic degeneration should enable a correct microscopic diagnosis in almost 100 per cent. of severe fatal diabetic cases. Increasing thoroughness of dietetic treatment will hinder such diagnosis by abolishing hydropic degeneration, but will greatly facilitate it by preventing deaths in mild cases, which are the ones that offer the only serious difficulties. The present series affords no example of a strictly normal pancreas with diabetes. If such an example should ever be demonstrated, it would presumably represent only unusually complete repair following

a diabetogenic inflammation, from which almost always some traces at least of fibrosis remain. But a large functional element must be recognized, which even under the most ideal conditions will hinder an infallible diagnosis of diabetes by any methods of pathologic study now available.

EXPERIMENTAL STUDIES IN DIABETES.

SERIES III. THE PATHOLOGY OF DIABETES.

9. LITERATURE AND DISCUSSION.

By FREDERICK M. ALLEN.

From The Physiatric Institute, Morristown, New Jersey.

The literature of diabetic pathology was reviewed by the writer in 1913¹ and 1919². Special reference should be made to Heiberg's³ admirable compend of the clinical pathology of the pancreas, embodying the results of long and careful individual investigations coupled with clear critical judgment and insight.

The present paper will consist of a partial survey of literature bearing upon the theory of infectious or toxic damage of the pancreas as the cause of diabetes, touching the salient publications sufficiently to obtain orientation of the results of this series of researches in relation to the work of previous authors. This discussion will comprise five topics, as follows:

- I. Clinical origin of diabetes in general or local infections.
- II. Frequency of pancreatic lesions.
- III. Etiologically significant findings in the diabetic pancreas.
- IV. Hydropic degeneration.
- V. Clinical-pathological correlations.

I. CLINICAL ORIGIN OF DIABETES IN GENERAL OR LOCAL INFECTIONS.

Ignoring baseless speculations of diabetes as a specific contagious disease⁴, due credit should be given to F. Hirschfeld for the first clinical suggestion of pancreatitis as the cause of diabetes. As far back as 1890, Hirschfeld⁵ described a group of cases in which diabetes was associated with the digestive disorders characteristic of failure of the external pancreatic function. Attacks of colic sometimes preceded the diabetes

by years. Impressed by these observations, and by autopsy reports of pancreatitis even in cases with no history of digestive disturbance, Hirschfeld⁶ carried on clinical studies of the question through a number of years. In 1905 he described 3 cases (out of 14 observed) of diabetes accompanied by symptoms interpreted as indicating pancreatitis, and attempted even in the absence of digestive trouble to differentiate the abdominal pain or pressure sensations of such cases from cholecystitis, ulcer and other conditions. In 1908 he proceeded to the clear hypothesis of infectious pancreatitis as the cause of diabetes, on the basis of 3 cases of diabetes combined with symptoms of pancreatitis following acute infections, chiefly influenza. He also suggested that chronic pancreatitis often results from acute pancreatic infections, which may be revealed by no clinical signs at the time. His position was weakened, however, by the co-existence of other factors, especially a strong diabetic heredity, in his cases. In 1909 Hirschfeld presented additional evidence (especially a case with diabetic heredity in which diabetes followed influenza) in support of his view that diabetes is caused in predisposed persons by pancreatitis set up by infection carried not merely through the ducts but also through the blood.

Hirschfeld acknowledged the indecisiveness of all clinical evidence of this sort, and his theory found far more numerous opponents than supporters. Reports of diabetes beginning in significant sequence to an acute infection now constitute a considerable literature. Reference may be made to Naunyn⁷, Heiberg³, Stengel⁸, Woodyatt⁹, and Motzfeldt¹⁰. It is uncertain whether the transitory glycosurias reported with many infections^{8, 11} are indicative of pancreatitis. The acute ailments under chief suspicion are tonsilitis and all other infections with pyogenic cocci, influenza, and the acute exanthems and septicemias. Subacute injuries, in the form of repeated exacerbations of infections of the biliary tract and other neighboring organs, are undoubtedly prominent in the etiology of pancreatitis, as shown in the following section, but this invasion is chiefly interlobular and probably does not produce diabetes in the majority of cases. True chronic pancreatitis appears to be rare as a cause of diabetes. Castronuovo¹² and several French writers have suspected syphilis, tuberculosis and chronic paludism as responsible for diabetes. Tuber-

culosis and malaria, however, may be practically excluded on the ground of recent evidence. Congenital syphilis gives rise to a typical pancreatitis, and is the commonest cause to suspect for marked pancreatic sclerosis in the fetus or new-born infant¹³; but it is seldom associated with diabetes, presumably because of the distribution and type of the lesions and possibly the general cachexia. Acquired syphilis rarely attacks the pancreas, as agreed by Wile¹⁴ and nearly all other authorities. Textbooks of diabetes mention occasional instances in which the diabetes has been benefited by treatment of the supposedly etiologic luetic infection. Carnot and Harvier¹⁵ and Gross¹⁶ have recently described definite examples of diabetes due to syphilitic pancreatitis. Warthin¹⁷ believes latent syphilis, even with continuously negative Wassermann reactions, to be a prevalent cause of diabetes, but this view has not been generally accepted¹⁸.

With regard to diabetic heredity, Heiberg¹⁹ quotes the hypothesis of Carnot that certain families are specially subject to pancreatic infections, by reason either of gross structural peculiarities or an unknown predisposition. This conception promises to be the fruitful one for future study of this problem. Careful autopsies of both the diabetic and non-diabetic members of diabetic families will be important for this purpose.

II. FREQUENCY OF PANCREATITIS.

The pancreas, which until recently was the most neglected of all the important viscera in pathology, diagnosis and therapy, is now becoming a subject of active interest and investigation in all these aspects. The facts elicited already demonstrate that it is one of the most commonly diseased organs in the body, and lend support to the above doctrine of the etiology of diabetes in pancreatitis. Whipple²⁰, in a series of 230 unselected autopsies, found the pancreas strictly normal in only 105. In a few instances acute pancreatitis was present in a degree which might readily give rise to subsequent diabetes, though in none of the cases were symptoms suggesting pancreatic trouble noticed during the observation of the patients in the Johns Hopkins Hospital. The preceding paper corroborates this high incidence of pancreatitis.

Disregarding such direct agencies as trauma, perforation of

a gastric or duodenal ulcer upon the pancreas, or invasion by an adjoining neoplasm, it may be said that pancreatic lesions are due to infectious or toxic matter conveyed by the blood, the lymphatics, or the ducts.

The blood route is probably the most frequent one, according to three-fold evidence. First, the recent study of Parker²¹ indicates that almost all systemic infections and intoxications of sufficiently great severity are attended with demonstrable pancreatic damage, though in the majority of instances this is limited to scattered focal necroses which probably have no important consequences. Second, observations of diabetes following acute infections were mentioned in the preceding section, and it is fair to assume that a larger number of pancreatic injuries occur, of less extreme degree, which give rise either to no diabetes or to long delayed diabetes. Heiberg²² was able to collect 18 references to pancreatitis with mumps, and Gross¹⁶ has added a recent example. Third, the frequent hyalin changes in the pancreas are presumably due, according to current views, to blood-borne toxins; furthermore, all cases of specific or nearly specific fibrosis of islands of Langerhans with little or no change in the acinar or interlobular tissue may be regarded as of circulatory origin. It seems probable that the majority of severe cases of diabetes, especially in young patients, are due to injuries through the blood path. The preponderant source of damage in the milder diabetes of elderly patients is more doubtful.

There is no doubt that pancreatic lesions find origin both through the ducts and through the lymphatics, but the relative importance of these two sources is under debate. Injury through the ducts, either by infection or by toxic secretions, is the older doctrine, which dates from the injections of fats and other substances into the ducts by Claude Bernard and his early successors, which has stimulated much experimental work²³, and which is still dominant in France²⁴. Inasmuch as occlusion of the ampulla of Vater by gallstones, causing injection of the pancreatic ducts with either sterile or infected bile, can account for relatively few cases of pancreatitis, the question has come down chiefly to spasm of the common duct sphincter with resultant forcing of bile into the pancreas, as maintained especially by Archibald²⁵, or simple ascending infections of the pancreatic ducts in consequence of biliary or

duodenal infections, as conceived by some of the French authors. The newer theory of lymphatic infection, especially by a retrograde transmission from the gall bladder to the pancreas, has received strong support from Arnsperger²⁶, Deaver²⁷, and Judd²⁸. According to the latter writer, "cholecystitis is nearly always associated with a certain grade of hepatitis or pancreatitis, or both". It now appears probable that a large proportion of cases of pancreatitis secondary to infections of neighboring viscera will be explained by lymphatic transmission.

It is easy to understand that injuries through the ducts may affect the entire pancreas, and though they involve the acinar tissue primarily, in the more severe forms they may damage the islands sufficiently to set up diabetes. A well recognized position is held by pancreatic calculi, which, though relatively rare, give rise in a majority of instances either to diabetes or well marked lowering of the glucose tolerance²⁹. Infections carried through the lymphatics involve primarily the head of the pancreas, and even if generalized throughout the organ are interlobular in distribution, so that the islands are usually not injured sufficiently to cause diabetes. Apart from the question of diabetes, these two classes of injuries, through the ducts and through the lymph channels, are responsible for the great majority of the pancreatic troubles which interest the surgeon and for very numerous obscure digestive complaints which are beginning to receive proper attention from internists. The activity in this field can be evidenced by a very incomplete list of recent papers on the diagnosis and treatment³⁰. From the standpoint of diabetes, three points may be specially noticed.

A. As the majority of cases of pancreatitis diagnosed clinically or of pancreatic sclerosis found postmortem are the results of injuries through the ducts or lymphatics, the frequent absence of diabetes is readily explainable. Due attention should also be paid to the suppression of diabetic symptoms by the impaired food absorption and emaciation which generally accompany an advanced destruction of pancreatic parenchyma. Blood sugar analyses and the more accurate glucose tolerance tests based upon them are one valuable diagnostic aid in cases of suspected pancreatic trouble.

Accurate clinical studies of this kind, combined with accurate postmortem examinations, will go far toward clearing up the supposed discrepancies between pancreatic lesions and carbohydrate assimilation.

B. As a rule, acute pancreatitis is nearly or quite symptomless, if occurring alone, and if coexisting with some general or local infection is generally obscured by the symptoms of the latter. The origin of diabetes from such inflammations is therefore traceable clinically in only a small minority of cases. Acute pancreatitis in the surgical sense is practically limited to the few cases of necrosis or suppuration. These are most important from the diabetic standpoint for the information which they afford concerning the proportion of the human pancreas which must be destroyed to produce diabetes, or in other words the margin of safety of the internal function of the pancreas. Recent case reports have added to the former scanty data on this subject. Hoffman's³¹ patient died within 24 hours after removal of two-thirds of the pancreas, and even with severe inflammation in the remnant the state of prostration would be a sufficient reason for absence of glycosuria. Gokal Chand believed that he had removed the entire pancreas of a two year old child, who was still living two years after the operation on a high carbohydrate diet without diabetes; but the pathological report by MacKenzie³² showed that only a part of the organ was actually removed. Sweet³³ described a large slough, in a case of acute pancreatitis; "it seemed as if most of the gland came away, but the patient suffered no ill effect". The best case is that of Mason³⁴, who removed approximately three-fourths of the pancreas according to his estimate in May, 1915, and the woman remained free from glycosuria at the time of his writing in 1918. According to this evidence, one-fourth of the human pancreas, even if somewhat damaged by inflammation, may suffice to prevent diabetes. It is evident that surgeons should make as careful estimations as possible of the amount of pancreatic tissue removed or remaining in such instructive cases, that the operative conditions may make estimates erroneous as in the case of Gokal Chand, that blood sugar analyses and accurate assimilation tests should be performed after recovery not only in such cases but in all known cases of pancreatitis

for both theoretical and therapeutic reasons, and that prolonged observation and postmortem examination may be necessary for a final decision, as illustrated by case No. 8 in section II of paper No. 7 of this series.

C. In this Institute, the experience of Mitchell³⁵ indicates that sufficiently careful history taking will in a fair minority of cases elicit some suggestive relation between diabetes and an antecedent infection or digestive symptoms which are more or less characteristic of pancreatitis. The observations of Sherrill³⁶ and John³⁷ make it probable that the majority of cases are preceded by a latent or prediabetic period, frequently years in duration, during which the impaired carbohydrate assimilation can be diagnosed by glucose tolerance tests. By reason of this interval, all apparent connection with the original inflammatory cause is lost, and the diabetes may remain quiescent until made active by later infections (Stengel⁸), obesity (Joslin³⁸) or gluttony or other functional or organic injuries of islands of Langerhans (Allen³⁹).

III. ETIOLOGICALLY SIGNIFICANT FINDINGS IN THE DIABETIC PANCREAS.

A. *Gross changes.*—The first disappointment in the modern study of diabetic pathology was found in the fewness of cases with gross atrophy or destructive processes in the pancreas, and the normal size and appearance of the organ in the vast majority. Heiberg⁴⁰ cites reports showing the size of the non-diabetic adult human pancreas to range from 34.9 to 115.6 gm., and also refers to hypertrophy of the pancreas to 150 gm. (Carnot) and 162 gm. (Schirmer). An excessively large pancreas with diabetes was found in Krumbhaar's⁴¹ dog. Also Heiberg⁴² observed transitory diabetes in a pneumonia patient, and at death from delirium tremens $2\frac{1}{4}$ years later the pancreas weighed 105 gm. and was normal microscopically except for reduction of the number of islands. It was found experimentally in paper 6 of this series that inflammation in the pancreas remnants of dogs may give rise to either atrophy or hypertrophy. Accordingly, the variations above mentioned in the size of the human pancreas may represent not always inborn abnormalities but sometimes the consequences of inflammation.

The reduction in gross size and weight of the pancreas with various forms of emaciation and cachexia is connected with histologic changes which in the extreme forms may make the specimens almost unrecognizable as pancreatic tissue. Oertel⁴³ has given careful descriptions of such changes in cachectic diabetic patients, and has added valuable details not formerly described. Similar and equally marked involution, however, was described and pictured by the writer⁴⁴ as a consequence of simple fasting in animals, and this same phenomenon is the basis of the erroneous belief of several writers that fasting produces transformations of acinar into island tissue. In human pathology, also, full endorsement can be given to the judgment of Heiberg⁴⁰ that a specific pancreatic atrophy without fibrosis does not exist, and that no such condition is concerned in the etiology of diabetes.

B. *Errors in microscopic study.*—Any intelligent appreciation of the microscopic pathology of diabetes requires a clearing away of the numerous errors which encumber the literature. In large measure these have been due to inexperience with the peculiarities of the pancreas, and to the use of material which was not sufficiently fresh or well fixed. The correlation of clinical and anatomic conditions has also often been mistaken, diabetic cases being regarded as very severe merely because of acidosis or early death in coma, when in fact the acidosis was the result of wrong diet, the diabetes inherently mild, and the potential tolerance high. But undoubtedly the worst confusion has resulted from the simple failure to distinguish accurately between the different types of cells in the pancreas, and it must be frankly recognized that not merely beginners but many persons who rank as authorities in pathology have no clear perception of the differences between acini, islands and ducts. Without claiming that this differentiation is easy or that the distinction can be infallibly made in every pancreas specimen, it may be pointed out that the greatest mistakes can be avoided merely by keeping in the difficulty carefully in mind. Oppel⁴⁵ properly emphasized the necessity of precision regarding islands; "Was nicht vollkommen intertubulären Zellhaufen entspricht, sollte man auch nicht als solche bezeichnen". Bensley⁴⁶ in connection with his special staining method repeated the warning. Just

as in another phase of diabetes so many writers have gone so far astray through failure to draw a precise line between glycosuria and diabetes, so also it will be noticed that nearly all the errors and contradictions encountered in a review¹ of pancreatic anatomy and pathology are traceable to this fundamental confusion between island and acinar tissue. Special attention in this connection may be directed to three topics, namely transitions between acinar and island tissue, selective preservation of islands after duct ligation, and certain clinical-pathological observations.

1. Transitions and transformations of acini into islands and vice versa were claimed by such experienced and painstaking workers as Lewaschew and Laguesse, and corroborated by an imposing array of their followers under a variety of physiological and pathological conditions in animals and man⁴⁷. The French clinical literature still mentions them as if they were a customary and fully demonstrated phenomenon⁴⁸. The opponents of this view have been equally numerous and active, and the introduction of the specific staining methods for the island cell granules seemed to have overthrown the transition theory definitively⁴⁹. As Saguchi⁵⁰ has again raised the question by these very methods, his work requires examination in some detail. Studying the pancreas of *Rana temporaria*, he found that the island cell granules are best revealed by fixation with Zenker fluid and staining with Heidenhain's iron-hematoxylin. The acetic acid in the fixative does not dissolve the granules but rather favors their fixation. "Not all the islet cells contain the minute granules which have been regarded as specific of them". Nevertheless, "the specific granules are the only bodies of which we should take account in characterizing any islet cell, other properties being of a rather negative nature, as Bensley pointed out". Saguchi distinguishes at least five types of island cells, namely a, b, and c types among the granular cells, and d and e types among the non-granular cells, also various transitions between these types of island cells, and transitions and transformations between acinar and island tissue. He considers the specific islet cell granules to be mitochondria, and finds other formations, namely lipid corpuscles and "urano-argentophile" granules,

which he regards as representing the internal secretion of the islands. Notice may be taken of three points particularly.

First, Saguchi evidently has placed too great reliance upon mere morphologic appearances in interpreting the nature of the island granules, being unaware of the diabetic experiments which indicate their internal secretory character. He seems, however, to have thrown valuable light upon certain details. Small vacuoles in the island cells have been described by several authors, and Laguesse was of the opinion that these were filled with a clear, apparently gummy fluid. It would be possible to imagine that these represent liquefied secretion, ready to be discharged, and that the hydropic change consists in a pathological exaggeration of this normal process. It appears, however, from Saguchi's observations that these vacuoles merely result from the dissolution of the lipoid corpuscles by the reagents used. Also, in demonstrating the specific character of these corpuscles, he has overthrown the assumption of early authors that they represented fatty degeneration of functionless cells.

Second, Saguchi deduces from certain morphologic appearances that the acinar cells have an internal in addition to their external secretory function. As previously pointed out (No. 1 of this Journal), such studies are valuable, and no longer stand in any contradiction to the doctrine of the specific and exclusive function of the islands in carbohydrate metabolism. Other structures which need investigation are the centro-acinar cells, concerning which Ogata, Kowakita and Oka⁵¹ have written a paper to which the writer has not as yet had access.

Third, if the possibility be conceded that transformations of cell types occur in such a low species as the frog, the demonstration still stands that in mammals not only are transitions of acini into islands and vice versa non-existent, but even the alpha and beta cells of the islands are not changed one into the other. A certain degree of post-embryonic formation and regeneration of islands from ducts has been demonstrated by authors including Bensley, and is evident sometimes with pancreatitis or diabetes (paper 6 of this series). Multiplication of island cells by mitosis was observed in the normal frog pancreas by Saguchi and in the toxin-damaged human pancreas by Parker²¹. The urgent need for islands in

diabetes should give rise to their formation from acini, if such a process is possible. The present writer is one of many who regard the claims of such changes in the diabetic human pancreas as erroneous, and this negative view is confirmed by the negative findings in careful studies of animal tissues at all stages of diabetes. Not only are the island cells always distinct from acinar cells, but also the alpha and beta cells of the islands remain distinct. Granting these facts, a different interpretation could be supported only on the unfounded assumption that some abnormality in diabetes inhibits the formation of islands from acini. Idle speculations of all kinds have long been troublesome in clinical diabetes, but a mysterious dyscrasia can scarcely be assumed in consequence of a simple resection of pancreatic tissue in a normal animal. Irrespective whether the animals were kept symptom-free on regulated diets or were fed so as to maintain active symptoms and downward progress, the alleged transitions have not been found; and when islands have become greatly reduced in number and size by hydropic degeneration, they remain thus reduced in patients and animals alike even through periods of years.

2. *Selective preservation of islands after duct ligation.*—One of the strongest proofs of the island theory has generally been sought in the absence of diabetes after ligation of the pancreatic ducts, when the acinar tissue atrophies and the islands supposedly remain. Accuracy requires that the defects of this evidence be recognized. Bensley has observed the persistence of islands in the ligated pancreas of the guinea pig, with successive stages of degeneration and regeneration, and Kirkbride⁵² also clearly demonstrated their intact state after the disappearance of acinar tissue. Kamimura⁵³ has obtained similar conclusive results in experiments on about 100 rabbits. By the fifth week after ligation he found practically the whole parenchyma replaced by connective tissue; after 10 weeks he noted contraction of the connective tissue and the appearance of some fat cells; and after about 15 weeks the connective tissue was almost wholly replaced by adipose tissue. The islands remained intact throughout. He furthermore proved that the animals developed no spontaneous glycosuria or hyperglycemia, and that their carbohydrate assimilation re-

mained normal as judged by test doses of glucose intravenously and by the degree of hyperglycemia produced by epinephrin, diuretin or hemorrhage. Species such as the rabbit and guinea pig are characterized by thin strands of pancreatic tissue widely spread through the mesentery and peritoneal fat. Perhaps this may be the reason why their acinar tissue becomes replaced by fibro-fatty formations and the islands are thus able to persist. But the flaw in an otherwise perfect proof is that for this same reason nobody has ever yet succeeded in producing diabetes in these species. Just as these species differ from the carnivora in their freedom from digestive disturbances after pancreatic ligation, because of the adequate function of other digestive glands, opponents may argue that the possibility of vicarious function of other organs for the internal pancreatic function remains open, and that the absence of diabetes when only the islands of the pancreas remain can serve as conclusive proof of the specific island function only in species which are known to be susceptible to diabetes from removal of the entire pancreas.

In the dog and all other species that have yet been made diabetic, the degeneration of the acinar tissue which follows duct ligation is accompanied by a dense sclerosis which destroys the islands by strangulation. Undoubtedly island tissue persists for long periods, as proved by the prolonged absence of diabetes, though the metabolic deficiency might be more evident if the digestive power were better. It has yet to be proved that island cells can be positively distinguished by the special stains under these circumstances, and the identification of the beta cells by their hydropic changes as shown in Figures 2 and 3 of paper No. 6 of this series illustrates the impossibility of recognizing them with older methods. MacCallum^{5,1} was unable to state positively that the atrophic tissue in the ligated pancreas remnant of a dog consisted solely of islands, and from the literature and from personal studies the writer is convinced that the numerous claims of selective preservation of islands in the dog are errors, due to the fact that groups of involuted acinar cells, which are small, rounded, lacking in acinar arrangement or zymogen content, and crowded together by enveloping fibrous tissue, have loosely been called islands by otherwise careful workers who are not sufficiently on their guard against such counterfeits. As a recent example

may be cited the work of Langfeldt⁵⁵, which is exact in most particulars and also was performed under competent histologic advice, and yet his Figure III, which is supposed to show preservation and proliferation of islands, clearly depicts (in the present writer's opinion) involuting acinar tissue. Similar criticism may incidentally be levelled at Apolant's⁵⁶ claim of a specific chemotherapeutic destruction of acinar tissue with preservation of islands in mice. His accompanying figure is too diagrammatic for a demonstration, and by its unlikeness to the normal architecture of mouse islands suggests that the formation in question may consist of involuted acini or proliferated ducts.

3. *Clinical-pathological observations.*—This discussion will attempt to sift the assertions regarding (a), preservation of islands in advanced pancreatic sclerosis and (b), hypertrophy or adenomata of islands.

(a) Selective sparing of islands amid advanced pancreatic sclerosis has been described particularly in cases of obstruction of the ducts by calculi. There are a number of published statements like that of Allen⁵⁷: "The microscopical report . . . shows an advanced stage of interlobular pancreatitis with the islands of Langerhans still well preserved, verifying Opie's observations that in this type the appearance of sugar in the urine occurs only at the very last stages of the disease". A painstaking study, with good illustrations, is that of Barron⁵⁸. Reference to this paper will show that Figures 1 and 2, from an ordinary case of severe diabetes, represent obvious islands of Langerhans with marked hydropic changes in some cells. Figures 9, 10, 13, 14 and 15, supposed to show islands persisting amid the scar tissue in a case of pancreatic lithiasis, are obviously different. The lack of typical architecture and the dark, opaque cytoplasm of the cells (possibly due to basophilic material) seem to indicate that these structures consist of involuted acinar tissue. It seems probable that the anatomic conditions in such cases will be found similar to those in the duct ligation experiments in dogs, and that the delayed outbreak or the relative mildness of diabetes in many such cases may be due chiefly to the digestive impairment and cachexia.

(b) The occurrence of moderate degrees of hypertrophy or hyperplasia of islands is probably disputed by no one, so

long as the increased islands retain fully typical appearances. Much confusion has resulted from autopsy reports of diabetic patients stating that islands were not only abundant but actually hypertrophic. Though MacCallum⁵⁹ spoke of hypertrophy in such a case, his article clearly pointed out the differences between the structures in question and true islands, and it is evident that he was dealing with "pseudo-islands", presumably consisting of altered acini or proliferated ducts. Fahr⁶⁰ gives definite ground for criticism in his colored plates. His Fig. 3 does not show branching and new formation of islands as alleged, but is a clear picture of involution of acinar tissue with some fibrosis. It is very questionable from the description and figures of B. Fischer⁶¹ whether he was dealing with hypertrophied islands as supposed or with altered acinar or duct tissue. Martius⁶² shows on his page 315 an illustration of apparently hyperplastic islands, but his claim that only a few individual acini are to be seen between the islands cannot be admitted, and the suspicion is thus raised that he has included involuted acinar tissue in his supposed islands. The atypical formations described and pictured by Gutman⁶³ are familiar to anyone who has studied much pathological pancreatic tissue, but there is good ground for Oppel's⁴⁵ criticism against designating them offhand as islands.

Horgan⁶⁴ has made an extensive and valuable study of the structures described by several writers as hypertrophic or adenomatous islands. In his entire series of 262 cases, hypertrophy of islands in connection with chronic pancreatitis was found in 48 cases, none of which showed glycosuria. The structures in question ranged in size up to 4 x 6 mm., and close connections were found between them and the ducts. Mention is made of use of the Lane-Bensley methods for recognizing islands, but it is not specifically stated that these structures were identified by this means. In particular, though it is stated that some of the cells were differentiated and others undifferentiated, there is lack of a definite statement as to whether they contained either alpha or beta granules.

Large, doubtful formations, such as shown in Horgan's microphotographs, are not a great rarity in diabetic autopsies, but their status as hypertrophic islands seems open to question, on the ground of the atypical arrangement of their cells in loops or tubes, and the complete absence of hydropic degener-

ation in any cases thus far observed even when the true islands were markedly hydropic. The possibility seems plausible that these structures and the tumors sometimes formed from them are composed of proliferated and altered duct cells, perhaps comparable to the duct proliferations shown in animal tissue in paper No. 1 of this series. Their internal secretory function is particularly doubtful. One point of valuable information from Horgan's work is that these formations may now be classified as a reaction to the organic injury of pancreatitis, rather than an attempt to meet the endocrine need of diabetes, as the interpretation has been heretofore.

C. *Etiologic lesions in the diabetic pancreas.*—As the attempt of French and other authors to distinguish a type of "pancreatic" as opposed to other types of diabetes failed, so also it has been impossible to demonstrate any uniform pathologic change as diagnostic of diabetes. The "granular atrophy" of von Hanseemann⁶⁵ may be summarized as a mixture of true or relative fibrosis with cachectic atrophy and involution and postmortem change. Herxheimer⁶⁶ still maintains a similar claim of a specific pancreatic cirrhosis. The writer has thus far not obtained the recent monograph by Seyfarth⁶⁷, but it is evident from brief Wochenschrift reports that he belongs to that majority of German pathologists who deny the specific endocrine rôle of the islands and even their existence as independent structures.

Opie's distinction between interlobular and intralobular (or interacinar or diffuse) forms of pancreatitis is universally recognized as valid in a broad sense, and the above criticisms against selective sparing of islands in advanced sclerosis obviously do not call into question the protection afforded to the islands by their central location in the ordinary grades of interlobular fibrosis. Heiberg³ likewise divides pancreatic changes roughly into those involving chiefly the islands and those involving chiefly the acinar tissue. But though the cases with almost specific damage of islands and sparing of acini are the ones which furnish the best evidence for the insular theory and are also most nearly diagnostic of diabetes, yet diabetes occurs with both forms of pancreatitis and sometimes with but little visible invasion of islands. With rare exceptions such as tumor, pigmentation (hemochromatosis), or acute inflam-

mation, the usual changes are fibrosis, hyalin deposit, and the peculiar "atrophy" of islands described by Weichselbaum⁶⁸. Such changes may, as Heiberg recognized, result from chronic infection, intoxication, or mechanical injury (stasis of secretion), or they may be the scars of acute inflammation and indicate merely that "a storm has passed over the islands". The condition described in this striking phrase is the one which is chiefly emphasized by the newer developments in diabetic pathology.

It being proved that the human pancreas is subject to frequent damage from infection or intoxication, and that the diabetic pancreas with few if any exceptions bears the marks of such damage, it remained only to supply the connecting link by imitating the assumed process in animal experiments.* As previously mentioned, such experiments reproduced and explained the most puzzling features of diabetic pathology, namely the existence of diabetes with a pancreas seemingly only slightly damaged in either acini or islands, by the demonstration of acute diabetogenic pancreatitis and the high degree of repair which may occur after subsidence of the inflammation with continuance of the diabetes. There is accordingly ground for the belief that the primary cause of diabetes is not necessarily continuous or progressive, and that, except for possible recurrences of infection or intoxication, no inherent tendency to aggravation need exist in many or most cases apart from the influence of food.

D. *Anatomic alterations of islands.* — Though Opie⁶⁹ laid the foundation of the theory of diabetes as due to disease of the islands of Langerhans, yet he admitted the existence of cases in which "the histological structure of the organ is unchanged". Numerous other authors have reported diabetic autopsies with little or no changes in the pancreas or its islands, and the vast majority of pathologists are known to be highly skeptical concerning any trustworthy basis for a microscopic diagnosis of diabetes. On the other hand the two stoutest champions of the island theory, Weichselbaum and Heiberg, who also have studied a greater number of cases than any

* Hugh H. Young and J. A. C. Colston (Journal of Urology, 1, 1917, 179) have reported a suggestive case of transitory glycosuria due to injury of the human pancreas in an operation upon the right kidney.

other individuals, maintain the existence of important island changes in every case of their long series. The former has emphasized particularly the qualitative changes and the latter the quantitative reduction of islands. Inasmuch, however, as Weichselbaum's series included 53 per cent. of cases of hydropic degeneration, and as this degeneration is one of the most important causes of reduction of the size and number of islands especially in the severest cases where islands are found fewest, the present knowledge that the hydropic change is a result and not a cause of diabetes serves to upset the most positive claims of either qualitative or quantitative island alterations as the demonstrable primary etiology of clinical diabetes.

Other points of difficulty may be discussed under the following three heads:

1. *Pancreatic lesions in non-diabetic cases.* — With extensive destruction of the pancreas by tumor or acute inflammation or necrosis, it is now generally recognized that absence of glycosuria may be explained by the actual survival of a sufficient number of functional island cells or by the accompanying prostration or cachexia. The same holds good for many cases of advanced pancreatic sclerosis with attendant indigestion, as already mentioned. Cecil⁷⁰ has shown that even the cases of fibrous and hyalin islands which he has described without diabetes are readily reconcilable with the island theory. At the same time there must be border-line cases in which it is impossible for the pathologist to decide positively whether the damage of islands suffices for diabetes or not, even apart from the large question of functional variations.

2. *Correlation of clinical and pathological study.* — As partially depancreatized non-diabetic dogs show some degree of lowering of their apparent sugar tolerance⁷¹, more accurate studies of the carbohydrate assimilation of human patients may resolve some doubts concerning the significance of pancreatic lesions. Wille⁷² in 1899 thus attempted to follow up Minkowski's animal experiments by a well planned investigation upon human patients. He gave a glucose tolerance test to every one of his hospital patients whose condition permitted, and then studied the pancreas of all who came to autopsy. He reported such tests on 800 patients, of whom 77 came to

autopsy. In 10 out of 15 cases with marked pancreatic lesions there was corresponding alimentary glycosuria, but there was also a considerable list of doubtful or irregular cases. The discrepancies may be largely explainable by the inaccurate methods then available; and today with blood sugar analyses for the tolerance tests and with attention directed to the islands rather than to the pancreas at large, a closer correlation may be anticipated. Allowances will still have to be made for the apparent lowering of tolerance with toxic states and its apparent elevation with cachexia or impaired absorption, but the recognition of various grades of pancreatic injury and of possible pre-diabetic states will be very different from the former crude classification into diabetic and non-diabetic cases.

3. *Quantitative deficit of islands at onset of diabetes.*—Aside from the careful counts of Heiberg⁷³ and others, the scarcity of islands of Langerhans especially in severe diabetes is generally sufficient to be noticeable in any careful autopsy. Knox⁷⁴ was impressed with this scarcity in a diabetic baby aged 9 months, and many such findings might be quoted in patients at all ages. Apparent exceptions will become much fewer when the precautions respecting identification of islands as mentioned above under section B are observed. Real difficulties, however, are encountered in milder cases, and especially in attempts to form a conception of conditions as they must exist at the earliest onset of most cases, when the food tolerance is still very high. Heiberg's contention that careful island counts will reveal a deficit in cases where it may be missed by a cursory examination is doubtless sometimes justified, but still is open to two criticisms. First is the difficulty of accurate enumeration of islands even by the most careful workers. For example, Clark⁷⁵ has calculated the data in the literature concerning the number of islands per cubic centimeter of pancreas as follows: Opie, 233 in head, 216 in body, 557 in tail; Laguesse, 1000; Sauerbeck, 1869; Dewitt, 1300 in new-born, 3142 in 4-year child, 1896 in adult; Heiberg, 1626 in head, 2583 in body, 3760 in tail. Clark himself applied the Bensley vital staining method to the human pancreas, and found a tremendous range of normal variation, namely from 2700 to 25,250 islands per gram of pancreas. If the attempt

be made to compute the actual mass of Langerhans tissue by reckoning the different sizes of islands, the difficulties in the way of accuracy are almost insuperable. The second objection is that the reduction in number and size of islands is so largely the result of hydropic degeneration, as already mentioned. It can therefore never be proved that the quantitative deficit of islands, when present, is the actual primary factor in the causation of the diabetes. The essential interest in quantitative estimations is therefore centered in certain early or mild cases, to decide whether diabetes may not be present in such cases with an actually greater mass of healthy appearing island cells than in certain other cases which are clinically non-diabetic. On account of the above mentioned difficulties, the present writer has never undertaken the labor of island counts, but believes, as stated in papers 7 and 8, that search of many sections representing all parts of the pancreas indicates that in some cases the existence or severity of diabetes is not explainable by a simple quantitative deficit of islands.

E. *Functional alterations of islands.*—The existence of a functional impairment of islands is made probable by two-fold evidence.

1. *Toxic and inflammatory reduction of island function.*—In certain experiments in paper 6, aseptic inflammation was found to produce diabetes in the presence of such masses of healthy appearing island cells as would otherwise suffice several times over to prevent it. The weakened function of these cells was further attested by their susceptibility to hydropic degeneration. In human diabetics it is a familiar observation that any febrile attack, from infection in any part of the body, lowers the assimilative power, often to very marked degree. If the weakened tolerance is overtaxed, the lowering of tolerance is likely to be permanent, presumably because of the usual hydropic degeneration. But if the blood sugar be kept normal by adequate restriction of diet during the attack, the tolerance afterward will often be found unimpaired. If it be admitted that an anatomic destruction of island cells during the attack and their regeneration afterward is improbable, such an observation affords proof of a functional impairment of the islands by intoxication.

2. *Response to treatment.* — As pointed out elsewhere⁷¹, it is found in partial pancreatectomies upon the dog and all other species that there is only a very narrow quantitative margin between the loss of pancreatic tissue which barely suffices to produce diabetes and the loss which produces an uncontrollable severity of diabetes. For example, something between seven-eighths and nine-tenths of the dog's pancreas must be removed to produce diabetes, and if more than nineteen-twentieths be removed it is generally impossible to control the diabetes or keep the animal alive on any diet. In the cat, diabetes is ordinarily prevented by one-fourth of the pancreas but not by one-fifth, while with one-tenth or even one-eighth of the pancreas the diabetes may be hopeless. If the evidence cited under section II B of this paper can be trusted, one-fourth of the human pancreas may also prevent diabetes, but other examples⁷⁶ indicate that diabetes will result if the remnant is much smaller than this. On the other hand abundant clinical experience proves that practically all cases of human diabetes are controllable by diet. Barring extremely rare exceptional cases and acute complicating factors such as coma or infections, this statement holds good even for the late stages of severe cases, after considerable loss of islands from hydropic degeneration must have occurred. The most instructive period, however, is the earliest possible one in any case, when the effect of the primary diabetogenic lesion can best be judged. It seems entirely incredible that an anatomic destruction in the pancreas (infectious or toxic in origin) should almost invariably fall within such narrow limits as to produce diabetes and yet not produce it in a degree of uncontrollable severity. From these facts it seems necessary to assume not a purely quantitative destruction but at least partly a functional injury of islands as the usual cause of diabetes.

IV. HYDROPIC DEGENERATION.

Besides the writers mentioned in paper 1, hydropic degeneration of the islands in diabetes has been observed by Ghon and Roman⁷⁷, Heiberg³, and Martius⁷². It is also sometimes recognizable in the plates published by authors who do not mention it specifically, as for example by Barron⁵⁸ and Winternitz⁷⁸, though the outlines of the vacuolated cells are

often missed owing to the rapidity with which their membranes break down postmortem. As it is a practically constant phenomenon in severe active diabetes, the failure of so many pathologists to find it is explained chiefly by the unfitness of their material because of late autopsies and poor fixation, also sometimes by the lack of severity in cases wrongly regarded as severe or under partial control by diet, and also partly by inadequate search. The significance of the process has already been sufficiently discussed, as a result not a cause of diabetes, as the basis of the irreparable decline of assimilation which occurs with excessive diets, and as the sole demonstrated example of anatomic breakdown of cells from over-stimulation of an internal secretory function.

It must be emphasized that the pictures of wide vacuolation represent actual rapid destruction of cells, therefore these marked changes can be expected only in the rapidly progressive diabetes of experimental animals and in human cases in a stage of intense symptoms and progressiveness. In intermediate cases or in those partially controlled by treatment, careful search of sufficient numbers of sections will often reveal occasional hydropic island cells. As the change is strictly specific, such a finding in fresh tissue, free from artefacts or other sources of error, in a single cell affords a positive diagnosis of diabetes. All present evidence indicates that under sufficiently thorough dietetic control, hydropic degeneration does not occur, because overstrain of the island function and accompanying decline of assimilation are avoided. Hydropic degeneration is also generally not visible in mild cases with active symptoms, or in any cases under treatment which limits the symptoms to hyperglycemia with or without slight glycosuria. Here the downward progress resulting from deficient dietary control indicates that hydropic degeneration occurs, but this decline is so slow, often extending over years, that the breakdown of island cells could necessarily seldom be seen unless the patient should die in an acute exacerbation.

As mentioned elsewhere⁷⁹, one factor in the severity of a case of diabetes, independent of the food tolerance at a given time, is its inherent progressiveness. If a typical young patient and a typical old patient start with equal hyperglycemia and glycosuria on the same diet, the former will lose flesh, strength and assimilative power rapidly and die within few a months or

years, while the latter will often experience slight if any symptoms while living from five to thirty years. Autopsy in the former case will show scarcity of islands and hydropic changes in those remaining, corresponding to the rapid march of the disorder. The latter may show fair numbers of islands with no visible hydropic changes in consequence of the years of excessive sugar. This difference is one of the best known facts in clinical experience, and at present the cause of the extreme variations in susceptibility to downward progress clinically or to hydropic degeneration anatomically is entirely unknown. The problem is made more complicated by the fact that in some elderly patients with minimum progressiveness of diabetes (including some hypertension or arteriosclerosis cases not clinically diabetic and only classed as such on the basis of hyperglycemia and subnormal sugar tolerance) the elevated blood sugar is difficult or almost impossible to reduce to normal, and yet seems to be nearly or quite harmless, while the same hyperglycemia in children without glycosuria entails fatal downward progress. The difference is not entirely one of age, for by operation puppies do not become more easily or more severely diabetic than old dogs; also there are wide differences between patients of similar age, so that severe and progressive forms of diabetes are sometimes seen in later life and "benign" or relatively unprogressive forms are observed in children.

Explanatory facts are so totally lacking that speculation may have some value, if only as an incentive to investigation. One possibility may be that young tissues are more susceptible to injury, so that the infections of youth generally entail a more serious anatomic and functional damage of islands. Another possibility may be that the diabetes seen in youth is that which has followed rather promptly upon severe pancreatitis, while slighter degrees of pancreatic injury pass unrecognized and only become manifest in the form of active diabetes many years later.

It seems furthermore conceivable that differences in the type of pancreatitis may be at least one factor. This suggestion is based upon the idea that the etiologic agent in youthful diabetes is generally blood-borne, and thus strikes the islands directly and not only partially destroys them anatomically but also renders them more susceptible to breakdown from func-

tional causes. The diabetes of later life is probably more often the result of duct or lymphatic invasions, which set up chiefly interlobular inflammation. With sufficient damage to the pancreas, diabetes may be produced and may even be severe as judged by a very low food tolerance, but the remaining islands still possess a sturdy functional power and offer a long resistance to functional overstrain. It may be guessed that older patients with the progressive type of diabetes may have suffered from an acute blood-borne pancreatitis similar to that of the young patients. A more definite clinical impression is that diabetes produced in young persons by interlobular pancreatitis, for example cases which originate from gallstones, are generally less progressive than other youthful cases.

This theorizing has but slender support and requires still further explanations or hypotheses. The healthy islands of dogs which become diabetic solely from operations are subject to very marked and rapid functional degeneration. Later papers, however, will show that the tendency to progressiveness differs in different species; and, as judged by the surgical cases heretofore referred to, the diabetes following partial pancreatectomy in man is less rapidly progressive than in the dog. An exception will also have to be made of the blood-borne toxins which produce hyalin deposits in islands, for these are often marked in elderly patients whose diabetes has been relatively mild and unprogressive, though they are occasionally found in younger and more severe cases. It may be suggested, however, that the hyalin material is a deposit along the small blood vessels, and it may therefore possibly be laid down either in damaged islands or in those the cells of which are normal except for this secondary interference with their nutrition. There is further a possibility that very mild blood-borne infections may cause relatively little functional injury to the islands, and that a severe acute pancreatitis originating from the ducts or lymphatics may damage the islands functionally as well as anatomically.

This entire line of speculation should be viewed with proper suspicion and should not be arbitrarily maintained or rejected, inasmuch as it touches the question which is at present the chief puzzle in diabetic pathology. In any event, the decision cannot affect the established facts regarding hydropic degeneration and its significance.

V. CLINICAL-PATHOLOGICAL CORRELATIONS.

As an accurate clinical record is essential to the proper study of the pathology in any diabetic case, so also an accurate pathological study carries certain consequences for the clinician. These have been discussed in the preceding papers and in former publications⁸⁶, and only the following three points will here be emphasized by repetition.

A. *Microscopic diagnosis*.—As already mentioned, the diagnosis of diabetes by the pathologist may be difficult or doubtful in mild cases, owing to uncertainties in gauging both anatomic and functional damage to the islands, especially in comparison with other cases of pancreatitis classed clinically as non-diabetic. As also mentioned, the confusion on this point will be lessened by greater clinical accuracy in the classification of diabetic cases and in the recognition of reduced carbohydrate tolerance in the supposedly non-diabetic cases. The greatest need for increased accuracy on the part of the pathologist lies in the proper estimation of slight fibrosis or other changes which may appear trivial in themselves but which may have importance as scars of a previous acute diabetogenic pancreatitis. In genuinely severe cases the microscopic diagnosis should be simple and positive, for with active symptoms there should be hydropic changes and with strict dietary control there should still be an unmistakable scarcity of islands.

B. *Downward progress*.—If a patient who is continuously faithful to treatment passes from a state of higher assimilative power to a state of lower assimilative power and finally dies, the pathologist should search carefully for a cause. Existing knowledge warrants dismissing old myths of constitutional or pluriglandular degeneracy, and the cause of downward progress should be sought in some progressive injury of the islands of Langerhans. The clinician is not excused by the finding of a nearly complete absence of islands at autopsy, if his dietary treatment has been such that the reduction can be attributed to slow hydropic changes from slightly overtaxed function. On the other hand, it is a possible assumption that when a pancreas has been sufficiently damaged anatomically or functionally the fibrosis will gradually advance or the

function will further deteriorate regardless of any available therapy. Against this assumption may be urged the fact that fibrosis is generally least in the youthful, most progressive cases, while the cases in later life show the most marked signs of damage from chronic or repeated subacute infections and yet are clinically least progressive.

C. *Criteria of treatment.*—The functional impairment which must be assumed in the origin of diabetes responds to dietary relief, and the observations to date establish a plain correlation between the clinic and the laboratory by the demonstration of extreme quantitative deficit of islands in every case of fatal severity. In addition to clearing up many former theoretical difficulties, this correlation has two practical applications.

1. If a patient dies of infection, disobedience to diet, or other accidental or intercurrent cause, his pancreas may show the characteristics of various earlier stages of diabetes, indicating a potential food tolerance in some measure proportional to the richness of islands. If he is faithful to diet and dies from hopeless severity of diabetes *per se*, the remains of functional island tissue in the pancreas will be so extremely scanty that the impossibility of continuance of life will be readily comprehensible. This pathological dictum may be resisted by many clinicians, because of the indictment of most forms of treatment through the indication that the vast majority of diabetic patients have died unnecessarily early, but it is the standard by which the treatment in this Institute is now being judged. Any exceptions will indicate a more profound functional impairment of islands than has yet encountered.

2. If a patient, from the time of his first coming for treatment, has proved unable to acquire tolerance for any living diet even by the strictest undernutrition, the finding of a nearly total absence of functional islands (i.e., islands free from Weichselbaum's "atrophy") is an excuse for the therapeutic failure. If there has been loss of tolerance under treatment, the explanation must be found either in functional overstrain for which the treatment is responsible, or in spontaneous downward progress. There have been too many extenuations of therapeutic mismanagement on glib assertions that diabetes is inherently progressive. The writer is convinced that

the great majority of diabetic cases, including most of those showing the most marked lesions of so-called "chronic pancreatitis", are not inherently progressive and can be controlled indefinitely by proper treatment. The question is open chiefly for the severest cases in children and young persons. There are reasons for believing that most such cases have originated in an acute pancreatitis, that the small scars remaining are merely signs that formerly "a storm has passed over the islands", and that the reason why pathologists have never found a progressive destructive process in such cases is that no such process exists. Beyond doubt the chief causes of downward progress are two: first and most important, hydropic degeneration due to overtaxed function; second, the known aggravating influence of large or small intercurrent infections. A spontaneous element possibly responsible for a very slow deterioration in some cases can be scientifically demonstrated only by experience with an adequate number of cases kept rigidly free from the two known factors mentioned, or with suitable allowance for such occasional factors. It is a mistake to suppose that the exclusion of a "spontaneous" cause means that all patients can be kept alive indefinitely. The extreme susceptibility of the worst cases to functional overstrain, the extreme difficulty of continuously avoiding such overstrain, and the dietary and infectious accidents in the history of most patients will often necessarily entail downward progress and death. Accurate proof on these points, however, in place of the loose guesswork and preconceived opinions heretofore prevailing, will explain the former mystery of a progressive clinical disorder without a demonstrated progressive pathologic process, and will clarify clinical conceptions by showing the chief causes of decline and by establishing a standard for judging methods of treatment which seek to prevent such decline.

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ALCOHOL IN THE DIABETIC DIET.

BY FREDERICK M. ALLEN AND MARY B. WISHART

*From the Hospital of the Rockefeller Institute for Medical Research,
New York.*

The essential innovation in the treatment of diabetes introduced by one of the writers consisted in the limitation of the total diet so as to relieve overstrain of the pancreatic function as far as can be determined by analyses of urine and blood. For the accomplishment of this purpose the restriction not only of carbohydrate-forming foods but also of total calories was recommended. Therefore one of the salient features in the new treatment was the limitation of fat.

As the harmful effects of a metabolic overload in the form of fat or calories are so gradual and insidious that they were practically unnoticed before, it was necessary to gather evidence by three methods, which were applied both to diabetic patients and to experimental animals^{1,2}. First, in very severe cases, symptoms were completely cleared up and it was proved that normal urine and normal blood sugar could be maintained for very long periods by the plan of limitation of total calories and corresponding limitation of body weight. The question is whether such cases can be improved in nutrition or strength by the addition of any food to the fixed diet without bringing a return of active diabetic symptoms. It was proved that the addition of fat causes a return of these symptoms, and owing to the severity of the cases this effect could be demonstrated rather quickly. Second, in milder cases it could be shown that longer periods of fat addition with corresponding gain in body weight brought on diabetic symptoms and damaged the assimilative power. Unless the damage had been prolonged to a point where it was irreparable, it was shown that reduction of fat feeding and of body weight restored the tolerance. Third, statistical evidence of clinical improvement and prolongation of life was afforded by a group of treated cases.

Parallel researches demonstrated that overstrain of the internal pancreatic function causes hydropic degeneration of cells in the islands of Langerhans, and thus explained the decline of assimilative power which has long been known to result when active diabetic symptoms are permitted to continue.

It was obvious at the outset, however, that no general conclusion can rest upon one special example. The principle that the diabetic organism is limited, in proportion to the severity of the diabetes, in its power to metabolize calories as such, or to carry an increment of body weight derived from any source, can be maintained only if supported by tests with other forms of food. Practically the only food material which is free from the special characters of carbohydrate, protein and fat, and which can be taken in sufficient quantities over sufficient periods of time, is alcohol. Tests with this substance were particularly desirable. First, it is universally accepted that ethyl alcohol is not directly convertible into sugar in the body, and the complication existing in the case of fat by reason of the glycerol in its molecule is thus avoided. Second, it is also believed that ethyl alcohol is not a direct former of the so-called "acetone bodies", as are the fatty acids of the fat molecule. Third, alcohol has been so widely recommended and used in the treatment of diabetes that the determination of its status is important from the practical standpoint.

As animals are less satisfactory for this purpose, tests were early begun upon patients in the Rockefeller Institute Hospital, but unfortunately had to be broken off like other phases of the clinical investigation. The observations obtained resembled those with fat feeding and were kept in mind in formulating the theory of the limitation of total calories, but they were not fit for publication until controlled and confirmed in certain aspects as had been originally contemplated. The publication of these experiments is now made possible by the studies of Leclercq. which appear simultaneously.

LITERATURE.

The scientific and social warfare over alcohol has produced such an enormous literature, as represented by the exhaustive bibliography of Abdelhalden³ in 1904, that only the scantiest survey is here feasible. The points requiring notice are its

food value, the possible toxic effects particularly on the pancreas, and its status with regard to glycosuria, acidosis and diabetes.

Possible toxic effects.—One section (p. 175) of Abderhalden's bibliography is devoted to the effects of alcohol upon the liver and pancreas. In a recent case report by Denéchau and Picard⁴, the pancreatic cirrhosis actually predominated over that in the liver, but the alcoholic etiology was merely assumed. The pancreatic alterations in alcoholic cases described by Symmers⁵ are of more doubtful character. In 31 cases of hepatic cirrhosis at operation Judd⁶ found pancreatitis in 12, and autopsy observations indicate a frequent association of the two⁷. From his clinical experience Strümpell⁸ regarded alcohol, especially in the form of beer, as responsible for cases of obesity, diabetes, gout, nephritis, and other disorders; but there is better ground for connecting the diabetes with the obesity than with any direct pancreatic injury from alcohol. A clinical association of diabetes with advanced cirrhosis of the liver is rare, perhaps because of the malnutrition accompanying the latter condition. Naunyn was impressed with the frequency of slight enlargement and tenderness of the liver among elderly well-to-do diabetics in private practice, and prolonged moderate alcoholic indulgence is one possible factor to be considered. The careful clinical studies of Cantani, Griesinger, Seegen, Külz, Frerichs and later textbook writers failed to establish alcoholic excess among the causes of diabetes. Glycosuria has been reported in connection with debauches, but it is evident that accompanying indiscretions of diet must be responsible, since alcohol alone never causes glycosuria. Such little suspicion as attaches to alcohol in any of the above connections holds only for very excessive or prolonged use, and the entire experience with alcohol administration in diabetes (reviewed below) excludes any fear that the results obtained in these experiments are attributable to any toxic action.

Food value of alcohol.—For the large and conflicting literature on this topic, reference must be made to general reviews such as that of Rosemann⁹. The general weight of evidence is that alcohol spares protein. Much of the confusion is on a par with that concerning fat; that is, though fat is an un-

doubted sparer of protein, there are conditions (for example, the sudden ingestion of large amounts of fat by a fasting subject, or the replacement of too large a proportion of carbohydrate in the diet by fat) when it temporarily does not reduce and may even increase the nitrogen excretion. Alcohol undoubtedly ranks with or below fat in this respect and not on a par with carbohydrate. Von Noorden¹⁰, summarizing experiments in his laboratory by Stammreich, concluded that alcohol spares protein on protein-rich but not on protein-poor diet. Authors in general recognize that, in addition to the composition of the diet or the metabolic state, habituation is a possible factor affecting the nutritive value of alcohol.

In respiration experiments Atwater and Benedict¹¹ had difficulty in gaining decisive results. Alcohol at least in some cases evidently furnished useful energy and spared fat, but as a protector of protein it proved inferior to carbohydrate and fat, and actual loss of nitrogen resulted in some instances. A recent investigation by Higgins¹² regarding the dynamic action showed that 30 or 40 cc. of alcohol left the heat production unchanged or in about one-fifth of the experiments increased it by only 5 to 7 per cent.

Mosenthal and Harrop¹³ have contributed the only accurate recent study of the food value of alcohol to diabetics. They concluded that "the addition of an equal number of calories of protein, fat or alcohol to a low caloric carbohydrate-free diet in cases of diabetes mellitus results in the assimilation of considerable amounts of nitrogen when the protein is used, a favorable nitrogen balance in only occasional instances with fat, and no change in the nitrogen equilibrium when alcohol is given". The test periods were no longer than 6 days, which according to Rosemann is the length of time which sometimes passes before the sparing action of alcohol becomes manifest. Also, as above noted, differences in the diet and metabolic state may influence the effects of alcohol.

Status with regard to glycosuria, acidosis and diabetes.—Continuity requires the discussion of these points together, because of the manner in which they are mingled in the literature.

Isolated mention may be made of the experiments of Höckendorf¹⁴, which seem to be the only formal tests of the

possibility of sugar formation from alcohol in phlorizinized dogs. Though the technique employed fails to meet the standards of modern criticism, the negative conclusion is so highly probable on general grounds that it has been accepted without question.

Up to the middle of the nineteenth century, the dietetic rules concerning alcohol were governed by prejudice or fancy. Even Claude Bernard thought that any supposed stimulant of the liver should be forbidden for fear of increased sugar production. Cantani and Bouchardat employed alcohol with appreciation of its food value, but all the early tests of its influence on diabetic symptoms were unreliable. Thus Günzler¹⁵ in Griesinger's clinic in 1856 asserted that wine increased glycosuria; but his diets were not properly regulated, and he also mentioned a profuse secretion of sugar-rich sweat. Rosenstein¹⁶ stated that coffee, beer and wine increased glycosuria, but that the increase from wine was less in proportion as its alcohol content was greater.

Külz¹⁷ concluded that alcohol in the form of dry wine diminished glycosuria, at least in one case. He exercised his usual care for the strict control of the diet, but the observed fluctuations of glycosuria were actually within the accidental variations of a mild case.

Von Jaksch¹⁸ found alcohol without influence upon febrile acetonuria. The diet is uncertain, because the role of diet was not then understood. Also there were no analyses for β -oxybutyric acid.

Hirshfeld did excellent work according to the possibilities of his time. In tests upon 2 non-diabetic subjects¹⁹, he added brandy representing 60 gm. alcohol on the 12th day of carbohydrate-free diet, and found no change in the acetonuria. β -oxybutyric analyses were lacking. In a series of diabetics²⁰, he maintained fixed diets of protein, fat and carbohydrate, and added alcohol for periods of 2 to 6 days. No effect was observed upon digestion and absorption of food, albuminuria or acetonuria, though the statement concerning acetone must be considered inadequate like the preceding. The sugar excretion was sometimes increased or diminished at first, but returned to the same general average, showing no influence of alcohol. The urinary nitrogen was at first slightly increased but later diminished, indicating a food value of the alcohol in sparing

protein. Except for the doubts concerning acetone, this work has permanent validity.

Neubauer²¹ reported that wine, representing 65 to 135 gm. alcohol per day, when added to diabetic diets had no distinct effect upon mild cases with trivial acidosis, but in more severe cases diminished both glycosuria and acidosis. His analyses were comprehensive, including the acetone of the breath and acetone, oxybutyric acid and ammonia in the urine. Also the differences in the figures with and without alcohol are often considerable. In order for the results to be accepted, it is necessary that studies with present-day accuracy shall confirm the reduction of glycosuria by alcohol. This is the crucial point, because the decline of acidosis could be readily explained by the mere fall in glycosuria. Neubauer's records specify merely "carbohydrate-free diet", with no details as to quantities. If the benefit of the doubt be given, by assuming that carbohydrate and protein were kept constant, it is still improbable under the conceptions then prevailing that fat was regulated with equal care. All the cases may be classed as mild or moderate in degree, and the changes reported may have been due to unnoticed variations in the diet or the accidental fluctuations in the course of mild cases. Unless the specific sugar-reducing action of alcohol can be confirmed, Neubauer's much-quoted work must be discarded. The apparent influence of alcohol in lowering blood sugar, however, makes the question of a temporary depression of glycosuria seem worthy of further investigation in mild and severe cases.

Benedict and Török²² kept diabetics on accurate mixed diets, and for test purposes substituted 372 to 744 calories of fat by the equivalent of alcohol. The result was said to be a reduction of both glycosuria and acidosis. The acetone values given for breath and urine are not a reliable measure of acidosis in the absence of β -oxybutyric analyses, but the urinary ammonia gives one useful measure. The most striking experiment was one (p. 342) in which, when fat was merely withdrawn, the acetone and sugar (but not the ammonia) increased, then when alcohol was added the acetone, sugar and ammonia diminished. This experiment gives ground for criticism, because it is not true in any general sense that undernutrition produced by omitting fat from a diet causes an increase of glycosuria or acidosis. This portion of the

results must have been accidental. The subsequent low figures may have represented merely a delayed effect of the undernutrition, or any other part of the results may equally have been accidental. To some extent this work can be judged by the same criterion as Neubauer's, namely whether it is true that alcohol reduces glycosuria. But the influence of fat is now better appreciated, and these experiments can at best prove no more than that alcohol perhaps creates less tendency to glycosuria and acidosis than the equivalent of fat. Alcohol was also found to spare protein better than fat; but the reduction of glycosuria and acidosis, whether due to the alcohol or to any accidental cause, would in itself account for a more favorable nitrogen balance.

Stäubli²³ had one patient free from glycosuria with moderate acetonuria on a standard ration with excessive fat and 60 gm. sodium bicarbonate daily. To this he added on 2 days 1750 cc. wine containing 10% alcohol. There was a distinct fall of both acetone and oxybutyric acid excretion, followed within the next 2 days by a still greater rise. Also on the second and third days after stopping wine there was a sudden glycosuria of 22.8 - 32 gm., which then ceased abruptly, with a corresponding drop in acidosis. Nothing is said of indigestion on the wine days, but on the succeeding days the patient was so ill that he could barely eat his diet, and blamed the unaccustomed wine. It is possible that the results were due to some abnormal drug action of the alcohol. General conclusions from one such case are unsafe.

Naunyn and other clinicians of his time used alcohol extensively both as a food and for a stomachic. Von Noorden²⁴ praised it highly as food and medicine (p. 299). He asserted that in some cases it reduces glycosuria. The one which he gave as the most marked example (p. 97) is not convincing; the differences might be accidental variations or especially the gradual improvement of a mild case under treatment. He also stated that his practical experience confirmed the acetone-reducing effect reported by Neubauer and others (p. 301), and he used the largest possible quantities of alcohol in combating coma (p. 388). It was said to exhibit actual life-saving power, and to be borne remarkably well by coma patients. The criticism may be made that many "practical experiences" in medicine have been inaccurate, and in more recent practice

alcohol not only seems to be useless against coma but also readily excites vomiting.

Higgins, Peabody and Fitz²⁵ performed tests upon themselves by taking 100 or 180 cc. whiskey on the fourth day of carbohydrate-free diet. "The acidosis was shown by a lowered CO₂ tension of the alveolar air, by an increased urinary excretion of ammonia nitrogen, and by acetone bodies and by the increased titratable acidity of the urine. The acidosis was accompanied by subjective sensations of malaise, an increased oxygen consumption, a negative nitrogen balance, increased pulse rate and increased ventilation. Alcohol given to the subjects on this diet in dosage comparable to that used for clinical purposes did not stop the progress of the acidosis or show any antiketogenic action. Coincidental with its administration there was further increase in the oxygen consumption and in the disagreeable subjective symptoms." The loss of nitrogen in the urine was very high (above 20 gm. daily, and comparable thus to the findings in severe diabetic acidosis) in all three subjects, and was not diminished by alcohol. There were the usual individual differences in susceptibility to acidosis on the identical regime; on the 4th day one subject excreted 0.69 gm. acetone bodies and 1.23 gm. ammonia nitrogen, while another excreted 2.95 gm. acetone, 20.27 gm. oxybutyric acid, and 4.8 gm. ammonia nitrogen. In all three the acetone bodies, which had proved resistant to alcohol, fell sharply with a single day of mixed diet, though the ammonia remained high. The total nitrogen fell markedly in two of them, but remained high in the one with the highest acidosis. These experiments were controlled by such complete analyses from so many different angles as to leave no doubt of the lack of an antiketogenic action of alcohol under the conditions chosen. The only questions that can be raised are whether the effects would be equally negative through a series of days or after habituation, and whether the results will be the same in diabetics as in normal persons. In a strict sense, this work confirms the reports of several previous authors concerning the negative influence of alcohol for reducing the acidosis of normal persons, and leaves the opposite claims concerning diabetic acidosis still open.

In beginning the treatment of severe cases of diabetes at the Rockefeller Institute Hospital, some use was made of

alcohol, particularly with a view to supporting the strength of dangerously weak patients during fasting or periods of very low diet. This incidental detail was curiously misunderstood by many persons, who imagined whisky to form an essential feature of the new treatment. Alcohol was never employed to any large extent in the diets, because of the belief in the necessity of restricting the total calories. It was soon discarded even during the initial period of weakness, as experience showed that collapse of strength was seldom to be feared and that coffee and broths were more agreeable and apparently more beneficial to the patients. The clinical experience with alcohol during this time created a strong impression that it alone was never responsible for hyperglycemia or glycosuria, even in diabetic cases of extreme severity, and thus harmonized with the accepted view that it is not directly converted into sugar. On the other hand, it was never observed to have any action in reducing ketonuria, as mentioned in a number of the case histories².

The experiments with alcohol were performed with the same methods and upon the same patients as those with fat. The methods therefore need not be recapitulated here, but the previous history of the two patients will be repeated briefly.

Patient No. 43²⁶, female, unmarried, age 27, was admitted to the Hospital on May 31, 1915, with severe diabetes of 4 months' known duration, but apparently dating from sepsis 3 years previously. Glycosuria was abolished and the diet built up to 1500 calories at discharge on June 1. Each time the patient was at home she broke diet more or less, and at her third admission, Dec. 2, 1916, her tolerance had fallen to approximately 50 gm. protein and 1100 calories, without carbohydrate. The weight, which at the first admission was 44 kg., also fell to about 33 kg. During the ensuing very long period in hospital, tests were performed with high caloric feeding, first with fat and then with alcohol additions. For the sake of completeness, the previously published table²⁷ of the fat experiment is here reproduced, and the alcohol experiment follows.

TABLE XI (*reproduced*).

Date.	Diet.					Weight.	Urine.			Blood plasma.			Remarks.
	Protein.	Fat.	Carbohydrate.	Alcohol.	Calories.		Volume.	Sugar.	Acetone bodies as acetone.	Sugar.	CO ₂	Acetone bodies as acetone per 100 cc.	
1917	gm.	gm.	gm.	cc.	kg.	cc.	gm.	gm.	per cent	vol. per cent	mg.		
May 14	60	103.0	—	—	1202	33.0	3510	0	1.49	—	—		
" 15	60	103.0	—	—	1202	33.4	5070	+	2.30	0.192	55.7	49.0	
" 16	60	103.0	—	—	1202	32.9	5075	5.04	1.71	—	—		
" 17	60	103.0	—	—	1202	33.8	5215	10.90	1.61	—	—		
" 18	60	103.0	—	—	1202	34.0	5200	10.40	2.24	—	—		
" 19	60	103.0	—	—	1202	34.3	5640	10.90	1.28	—	—		
" 20	Fast-day.					34.1	1895	7.22	1.03	0.213	64.5	21.8	
" 21	60	203.0	—	—	2132	34.8	3330	+	2.10	0.175	—	29.8	
" 22	60	253.0	—	—	2597	34.9	5720	+	7.01	—	—		
" 23	60	253.0	—	—	2597	34.6	4740	18.01	9.48	—	—		
" 24	60	253.0	—	—	2597	33.9	3205+	18.99	10.63	—	—		
" 25	60	253.0	—	—	2597	34.2	2680	18.52	9.58	—	—		
" 26	60	253.0	—	—	2597	34.2	2280	13.80	9.57	0.298	42.3	—	
" 27	—	30.0	—	—	279	34.6	2035	35.60	9.80	0.233	42.3	—	
" 28*	60	253.0	—	—	2597	33.7	1090	5.67	8.61	0.286	57.6	52.1	
										0.154	48.3	77.5	
" 29*	60	253.0	—	—	2597	35.6	2995	24.06	18.41	—	—		
" 30*	60	253.0	—	—	2597	34.4	3475	24.84	17.25	0.222	43.7	99.0	
" 31	60	10.0	—	—	332	35.4	5115	45.72	11.18	0.216	48.3	52.1	
June 1	60	10.0	—	—	332	34.9	5645	31.90	4.46	—	—		
" 2	60	10.0	—	—	332	35.0	4845	24.23	1.55	—	—		
" 3	Fast-day.					—	35.5	1575	8.80	1.31	0.228	57.9	40.8
" 4	"					—	34.8	860	+	1.29	0.170	58.9	42.3
" 5	60	4.0	—	—	282	34.4	4100	+	2.01	—	—		
" 6	60	4.0	—	—	282	34.6	4900	+	0.88	—	—		
" 7	60	3.0	—	—	275	35.4	5440	+	0.49	—	—		
" 8	60	3.0	—	—	275	34.9	3570	+	0.51	—	—		
" 9	60	3.0	—	—	275	34.5	4520	+	0.36	—	—		
" 10	Fast-day.					—	34.1	1855	+	0.31	0.208	64.5	43.1
" 11	59	—	—	—	249	34.4	4005	+	0.64	0.159	59.8	20.4	
" 12	59	—	—	—	249	34.4	4660	0	0.42	—	—		
" 13	59	1.0	1.0	—	255	33.0	4610	0	0.41	—	—		
" 14	59	1.0	1.0	—	255	33.4	4820	0	0.29	—	—		
" 15	59	1.0	1.0	—	255	33.8	4605	0	0.23	—	—		
" 16	59	1.0	1.0	—	255	34.2	5250	0	0.47	0.128	—	13.4	
" 17	Fast-day.					34.3	2230	0	0.54	0.200	67.3	—	
" 18	59	1.0	1.0	40	535	33.8	3640	0	0.18	0.113	—	26.6	

* 20 gm. sodium bicarbonate on this day.

TABLE I.
Case No. 43.

Date.	Weight	Diet.					Urine.				Blood Plasma.		
		Alcohol.	Carbohydrate.	Protein.	Fat.	Calories.	Volume.	Sugar.	Total N.	Total Acetone bodies.	Sugar mg. per 100cc.	Co2 Vol. %	Total Acetone bodies mg. per 100cc.
1917	Kg.	gm.	gm.	gm.	gm.		c.c.	gm.	gm.	gm.			
June 19	34.1	40	1	59	1	534	4960	Neg.	—	Neg.	—	—	—
" 20	35.1	40	1	59	1	534	5425	"	—	"	—	—	—
" 21	35.4	40	1	59	1	534	4815	"	—	"	—	—	—
" 22	35.2	40	1	59	1	534	6415	"	—	"	—	—	—
" 23	35.0	40	1	59	1	534	3130	"	—	"	—	—	—
" 24	34.6	50	Fast-Day.			350	3550	"	—	0.39	164	51.3	12.7
" 25	34.6	100	1	59	1	954	5490	"	—	0.28	72	67.3	30.3
" 26	35.0	100	2	59	1	961	5250	"	—	neg.	—	—	—
" 27	34.3	100	2	59	1	961	5260	"	—	"	—	—	—
" 28	35.5	100	2	59	1	961	5695	"	—	"	—	—	—
" 29	36.0	100	2	62	6	1040	5305	"	—	"	—	—	—
" 30	36.2	100	2	62	6	1040	5225	"	—	"	156	61.7	15.3
July 1	36.7	100	4	1	0.4	721	4035	"	—	"	131	59.8	—
" 2	35.3	100	6	69	7	1064	4250	"	—	"	—	—	—
" 3	35.2	100	6	69	7	1064	3930	"	—	"	—	—	—
" 4	35.2	100	6	76	12	1144	4330	"	—	"	—	—	—
" 5	35.2	100	6	76	12	1144	5195	"	—	"	—	—	—
" 6	34.9	100	6	76	12	1144	5830	"	—	"	—	—	—
" 7	34.9	100	6	76	12	1144	3390	"	—	"	—	—	—
" 8	34.5	100	4	1	0.4	721	3875	"	—	"	—	—	—
" 9	34.7	100	6	76	12	1144	6380	"	—	"	—	—	—
" 10	34.8	100	6	76	12	1144	3430	"	—	"	—	—	—
" 11	32.9	100	6	84	17	1227	4660	"	—	"	—	—	—
" 12	33.2	100	6	84	17	1227	4200	"	—	"	—	—	—
" 13	33.6	100	6	84	17	1227	3410	"	—	"	—	—	—
" 14	33.6	100	6	84	17	1227	3135	"	—	"	—	—	—
" 15	34.0	100	Fast-Day.			700	3135	"	—	"	—	—	—
" 16	32.6	100	6	84	17	1227	4225	"	—	"	—	—	—
" 17	33.0	100	6	84	17	1227	4265	"	—	"	—	—	—
" 18	33.3	100	6	84	17	1227	3695	"	—	"	—	—	—
" 19	33.6	100	6	84	17	1227	4616	"	—	"	—	—	—
" 20	33.5	100	6	84	17	1227	3570	"	—	"	—	—	—
" 21	33.6	100	6	84	17	1227	2535	"	—	"	—	—	—
" 22	33.5	100	Fast-Day.			700	3865	"	8.50	"	* 99	71.7	59.2
" 23	33.0	100	6	84	17	1227	4885	"	10.15	"	159	69.2	16.0
" 24	33.2	100	6	84	17	1227	5850	"	13.46	"	—	—	—
" 25	33.1	100	6	84	17	1227	4675	"	10.29	"	—	—	—
" 26	33.0	100	6	84	17	1227	4525	"	10.71	"	—	—	—
" 27	33.3	95	6	84	17	1192	5375	"	13.44	"	—	—	—
" 28	33.3	95	6	84	17	1192	3355	"	10.73	"	—	60.6	10.6
" 29	33.3	95	Fast-Day.			665	3315	"	9.94	"	238	70.0	6.6
" 30	32.8	240	6	84	17	2207	4700	"	13.63	"	109	68.1	17.4
" 31	33.3	190	6	84	17	1357	4740	"	13.27	0.81	—	—	—
Aug. 1	32.7	190	6	84	17	1857	5525	"	13.82	0.94	—	—	—

* At 4 p. m.

TABLE I.

(Continued).

Date.	Weight	Diet.					Urine.				Blood Plasma.		
		Alcohol.	Carbohydrate.	Protein.	Fat.	Calories.	Volume.	Sugar.	Total-N.	Total Acetone bodies.	Sugar mg. per 100cc.	Co ₂ Vol. %	Total Acetone bodies mg. per 100cc.
1917	Kg.	gm.	gm.	mg.	gm.		c.c.	gm.	gm.	gm.			
Aug. 2	32.7	190	6	84	17	1857	5680	"	13.63	1.70	—	—	—
" 3	33.3	190	6	84	17	1857	5560	"	13.37	1.52	—	—	—
" 4	33.3	190	6	84	17	1857	3608	"	10.82	0.94	—	59.8	17.3
" 5	33.9	200	Fast-Day.			1400	3813	"	11.06	—	238	67.3	23.7
" 6	33.0	200	6	84	17	1927	4432	"	11.08	—	130	69.2	29.5
" 7	33.5	200	6	84	17	1927	4730	"	13.72	—	—	—	—
" 8	32.5	200	6	84	17	1927	5600	Faint	15.68	—	—	—	—
" 9	33.6	200	6	84	17	1927	5155	"	13.40	—	—	—	—
" 10	33.5	200	6	84	17	1927	5197	11.40	14.55	—	—	—	—
" 11	33.6	200	6	84	17	1927	2282	5.93	12.55	—	217	59.8	32.4
" 12	33.4	—	Fast-Day.			3945	6.31	9.86	—	—	278	58.9	37.7
" 13	32.8	—	6	84	17	527	4945	34.62	14.84	0.74	228	67.3	44.2
" 14	32.8	—	6	84	17	527	4150	28.02	14.01	0.54	—	—	—
" 15	33.0	—	—	26	6	157	1955	neg.	8.60	0.33	—	—	—
" 16	32.7	—	—	15	11	159	3655	"	9.14	0.44	—	—	—
" 17	33.4	—	—	42	16	322	3853	"	—	0.42	—	—	—
" 18	33.5	—	—	42	16	322	3261	"	—	0.16	—	—	—
" 19	33.5	—	Fast-Day.			3138	—	—	—	0.50	—	—	—
" 20	33.2	—	—	50	1	214	5540	"	—	0.23	196	67.3	—
" 21	34.0	—	—	50	1	214	5540	"	—	Faint	—	—	—
" 22	33.5	—	—	50	1	214	4627	"	—	"	—	—	—
" 23	34.1	—	—	50	1	214	4075	"	—	"	—	—	—
" 24	34.7	—	—	50	1	214	4780	"	—	0.14	—	—	—
" 25	35.0	—	—	50	1	214	3505	"	—	0.28	—	—	—
" 26	35.0	—	Fast-Day.			4090	—	—	—	0.33	213	69.2	—
" 27	34.8	—	—	50	1	214	4510	"	—	0.18	137	78.7	—
" 28	34.3	—	—	50	11	308	4850	"	—	Faint	—	—	—
" 29	34.6	—	—	50	11	308	4440	"	—	"	—	—	—
" 30	34.2	—	—	50	22	404	4360	"	—	0.39	—	—	—
" 31	34.2	—	—	50	22	404	4135	"	—	neg.	—	—	—
Sept. 1	33.5	—	—	50	22	404	3690	"	—	0.26	—	—	—
" 2	33.0	—	Fast-Day.			3855	—	—	—	neg.	118	—	—
" 3	32.0	—	—	50	32	501	3810	"	—	"	116	66.1	29.0

SUMMARY OF RESULTS IN CASE NO. 43.

The first week of Table XI represents hyperglycemia and glycosuria which had come on in consequence of a preceding period of gradual additions of fat to the diet. The subsequent results are summarized as follows in the publication mentioned (pp. 525-526).

"The opportunity seemed favorable for testing whether this change represented 'spontaneous downward progress' on the part of the patient,

or whether it was merely the culmination of several months of diet slightly overtaxing the tolerance. A sudden addition of 100 gm. fat was made on May 21, with an additional 50 gm. on May 22, thus raising the total diet to 2600 calories. Marked and continuous glycosuria and ketonuria followed, as shown in Table XI and in the graphic chart. Also the total acetone increased in the blood plasma, and the alkali reserve fell as low as 42.3 per cent on May 26 and 27. The patient, who had welcomed the opportunity to eat more, quickly became unwell and unhappy. The daily administration of 20 gm. sodium bicarbonate on May 28, 29 and 30 seemingly lowered the blood sugar and urine on the first day, but had doubtful effect thereafter. It also raised the plasma bicarbonate temporarily, but by May 30 this was again down to 43.7 per cent in spite of the alkali dosage. It is also possible that this dosage may have been partly responsible for the maximum of 99 mg. total acetone per 100 cc. of blood plasma on May 30. Here also dyspnea was not present, but on account of general malaise the patient was glad to discontinue the fat ration.

"Accordingly on May 31 fat was eliminated from the diet as far as convenient, keeping the protein unchanged. The first effect was seen upon acidosis, in the fall of acetone bodies in blood and urine, the spontaneous rise of plasma bicarbonate, and the relief of the clinical symptoms. The sugar excretion rapidly diminished. The hyperglycemia was more stubborn, but there was a progressive diminution down to a normal level on June 18, following the fast-day of June 17. Thereafter it proved possible, as in the preceding patient, to increase the protein to 84 gm. daily without glycosuria."

Table 1 of the present paper represents the subsequent experimental period, in which the diet was kept as fat-free as possible while permitting a sufficient variety of appetizing foods. The protein was increased to 84 gm. as stated, and carbohydrate as high as 6 gm. was introduced, thus demonstrating the higher tolerance for sugar-forming foods. At the same time calories were introduced in the form of alcohol, for which whiskey was used up to July 27 and pure (95%) alcohol diluted with water after that date. The patient, though never accustomed to such beverages before, showed a remarkable tolerance for alcohol. Several similar experiments begun on other male or female patients had to be abandoned because sufficient quantities could not be taken without symptoms, but by distributing the doses every two hours this young woman was able to consume the large quantities mentioned without the slightest toxic indications. At first the alcohol gave the feeling of increased strength. Toward the end of the experiment a distaste was developed by the large dosage, so that the patient was glad to terminate the test. A slight loss in strength and well-being was probably attributable to the return of active diabetic symptoms, though less marked than in the experiment with fat. The body weight was not increased. The nitrogen balance was not determined, but the urinary nitrogen seemed to remain practically the same with the lower and the higher alcohol intake. The following remarks may be made

concerning (1) the effect on the sugar in blood and urine, (2) the acetone in blood and urine, and (3) the interpretation.

1. *Sugar in blood and urine.*—Up to July 23, even with the increased carbohydrate and protein, glycosuria remained absent and the blood sugar was constantly lower than at the close of the fat feeding test in Table XI. As the diet included 100 gm. of alcohol daily, this result in a patient with such severe diabetes confirms the current view that there is no direct sugar formation from alcohol. The diet of 1227 calories, however, was slightly above the known tolerance, and by July 29 a marked hyperglycemia of 0.238% was present. With the subsequent increase of alcohol to about 200 gm. daily and the corresponding increase of total calories to nearly 2000, the blood sugar by Aug. 12 had risen to 0.278%, and furthermore remained high during the fast-day instead of falling as on most former occasions. About this time also glycosuria appeared rather suddenly. The sharp reduction of calories by omission of all alcohol after Aug. 11 was not sufficient to stop it; on the contrary, it actually increased, according to the natural tendency when the tolerance in a very severe case has been damaged by prolonged over-feeding. Therefore omission of carbohydrate and a considerable reduction of protein was necessary for safety, and by this means glycosuria was quickly checked and the plasma sugar gradually reduced to normal.

2. *Acetone in blood and urine.*—The total acetone bodies (expressed as acetone) increased slightly in blood and urine in consequence of the long alcohol period. It is a safe assumption that if such a patient had been kept on the diet of 84 gm. protein and 6 gm. carbohydrate without alcohol, the acetone would not have increased and would probably have diminished. This experience, therefore, does not conform to the theoretical expectation that alcohol, by sparing combustion of fat, should reduce acetone formation. On the contrary, it gives a slight confirmation of the finding of Higgins, Peabody and Fitz that alcohol increases ketosis. Another interpretation, however, is that when the sugar tolerance of a diabetic patient is damaged by addition of any non-carbohydrate food, more or less increase of acetone production may be expected. Most instructive is a comparison with the preceding tests of high

fat diets in this patient, which showed a decided parallelism between the rise of fat intake and the rise of acetone. This result, therefore, serves to confirm the existing belief that there is no direct transformation of alcohol into acetone.

3. *Interpretation.*—There is room for criticism that the period from July 11 to 23 was not long enough to rule out an injurious effect of the increased protein, and that the whole result may be explained as a gradual overtaking of the tolerance by the 84 gm. of protein and 6 gm. of carbohydrate instead of by the increase in total calories. Other experience gives ground for believing that a diet limited to 84 gm. protein, 6 gm. carbohydrate and 17 gm. fat, without alcohol, would have produced an actual lowering of the blood sugar, and the opposite result here is accordingly ascribable to the alcohol. As the extensions and controls of this work which had been contemplated proved impossible, this interpretation is merely stated, and reference made to the following paper for support.

TABLE IX (*reproduced*).

Date.	Diet.					Weight.	Urine.			Blood Plasma.			Remarks.
	Protein.	Fat.	Carbohydrate.	Alcohol.	Calorie.		Volume.	Sugar.	Acetone bodies as acetone.	Sugar.	CO ₂	Acetone bodies as acetone per 100 cc.	
1917	gm.	gm.	gm.	cc.		kg.	cc.	gm.	gm.	per cent	vol. per cent	mg.	
May 7	70	131	—	—	1500	36.2	2615	0	+	—	—	—	
" 8	70	131	—	—	1500	37.6	2370	0	+	—	—	—	
" 9	70	131	—	—	1500	37.2	3080	0	+	—	—	—	
" 10	70	131	—	—	1500	37.1	3440	+	+	—	—	—	
" 11	70	131	—	—	1500	37.3	2860	0	0	—	—	—	
" 12	70	131	—	—	1500	36.6	2440	0	+	—	—	—	
" 13	Fast-day.					37.2	3100	0	0	—	—	—	
" 14	70	131	—	—	1500	36.2	2000	+	2.62	—	—	—	
" 15	70	131	—	—	1500	37.4	2582	0	5.73	0.208	72.0	31.0	
" 16	70	131	—	—	1500	37.5	2770	+	12.41	—	—	—	
" 17	70	131	—	—	1500	37.8	3142	++	17.58	—	—	—	
" 18	70	131	—	—	1500	38.0	3340	++	5.98	—	—	—	
" 19	70	131	—	—	1500	37.9	3152	++	3.18	—	—	—	
" 20	Fast-day.					37.2	2800	+	1.08	0.179	71.1	31.0	
" 21	70	231	—	—	2430	35.8	2413	+	5.70	0.246	—	34.7	
" 22	70	281	—	—	2895	37.4	2800	5.88	18.54	—	—	—	
" 23	70	281	—	—	2895	38.0	3480	10.26	17.32	—	—	—	
" 24	70	281	—	—	2895	37.6	3340	13.86	13.70	—	—	—	
" 25	70	281	—	—	2895	37.6	3630	16.29	18.65	—	—	—	
" 26	70	281	—	—	2895	37.2	3435	18.87	15.98	0.200	47.1	83.0	5:00 p.m.
" 27	—	100	—	—	930	37.2	3377	18.54	7.61	0.238	57.6	63.5	10:00 a.m.
" 28*	70	281	—	—	2895	36.4	1955	7.40	18.10	0.263	69.1	71.3	9:00 "
										0.208	63.5	89.2	6:00 p.m.
" 29*	70	281	—	—	2895	37.5	3483	26.13	25.01	—	—	—	
" 30*	70	281	—	—	2895	38.0	3448	22.87	49.73	0.216	57.8	108.0	5:00 "
" 31	70	11	—	—	391	38.2	3105	21.56	17.68	0.286	59.7	57.2	9:00 a.m.
June 1	70	11	—	—	391	37.9	2520	22.32	4.24	—	—	—	
" 2	70	11	—	—	391	38.3	2728	18.83	1.85	—	—	—	
" 3	Fast-day.					38.5	2155	8.36	0.67	0.303	69.2	12.6	10:00 "
" 4	"					38.2	2810	+	0.90	0.204	63.6	35.8	10:00 "
" 5	70	11	—	—	391	38.4	1760	+	0.81	—	—	—	
" 6	70	11	—	—	391	39.2	3052	+	0.81	—	—	—	
" 7	70	11	—	—	391	38.7	3030	+	0.33	—	—	—	
" 8	70	11	—	—	391	38.8	3000	+	0.18	—	—	—	
" 9	70	11	—	—	391	38.5	2790	+	0.50	—	—	—	
" 10	Fast-day.					38.6	3260	0	0.19	0.170	56.0	12.2	10:30 a.m.

* 20 gm. sodium bicarbonate on this day.

TABLE IX—*Concluded.*

Date.	Diet.					Urine.				Blood plasma.			Remarks.
	Protein.	Fat.	Carbohydrate.	Alcohol.	Calories.	Weight.	Volume.	Sugar.	Acetone bodies as acetone.	Sugar.	CO ₂	Acetone bodies as acetone per 100 cc.	
1917	gm.	gm.	gm.	cc.		kg.	cc.	gm.	gm.	per cent	vol. per cent	mg.	
June 11	70	11	—	—	391	38.1	2215	+	0.48	0.161	61.7	18.6	9:00 a.m.
" 12	70	11	—	—	391	38.8	2050	+	0.18	—	—	—	
" 13	70	11	—	—	391	39.9	3640	+	0.11	—	—	—	
" 14	70	11	—	—	391	39.7	3830	0	0.11	—	—	—	
" 15	70	11	—	—	391	39.3	3470	0	0.52	—	—	—	
" 16	70	11	—	—	391	39.0	3435	0	—	0.164	—	8.3	5:00 p.m.
" 17	Fast-day.					39.0	4110	0	—	0.182	67.3	—	11:00 a.m.
" 18	70	11	—	70	881	38.5	1728	0	0.13	0.141	61.7	13.0	9:00 "
" 19	70	11	—	70	881	39.9	3630	0	0.18	—	—	—	
" 20	70	11	—	70	881	39.8	3585	0	0.32	—	—	—	
" 21	70	11	—	70	881	39.4	3690	0	0.33	—	—	—	
" 22	70	11	—	70	881	39.0	2210	0	—	—	—	—	
" 23	70	11	—	70	881	38.6	3060	0	—	—	—	—	
" 24	Fast-day			100	700	39.0	4166	0	—	0.098	57.0	7.2	10:00 a.m.
" 25	70	11	—	100	1091	38.4	2104	0	0.23	0.066	72.1	19.1	9:00 "
" 26	70	11	—	100	1091	39.2	3340	0	0.23	—	—	—	
" 27	70	11	—	100	1091	38.4	3555	0	—	—	—	—	
" 28	70	11	—	100	1091	38.4	2975	0	—	—	—	—	
" 29	70	11	—	100	1091	38.6	3468	0	—	—	—	—	
" 30	70	11	—	100	1091	38.6	3685	0	—	0.12	55.1	11.1	5:00 p.m.
July 1	111	—	3.6	100	721	39.0	4030	0	—	0.11	—	—	10:00 a.m.
" 2	77	16.5	—	100	1170	37.6	1620	0	—	0.13	64.5	—	9:00 "
" 3	77	16.5	—	100	1170	39.4	3535	0	—	—	—	—	
" 4	85	22	—	100	1250	39.0	3640	0	—	—	—	—	
" 5	85	22	—	100	1250	38.2	3230	0	—	—	—	—	
" 6	85	22	—	100	1250	38.2	2882	0	—	—	—	—	
" 7	85	22	—	100	1250	38.0	3990	0	—	—	—	—	
" 8	111	—	3.6	100	721	37.8	3505	0	—	—	—	—	
" 9	85	22	—	100	1250	37.4	2678	0	—	—	—	—	
" 10	85	22	—	100	1250	37.2	4807	0	—	—	—	—	
" 11	95	22	—	100	1297	36.5	4225	0	—	—	—	—	
" 12	95	22	—	100	1297	36.3	2430	0	—	—	—	—	
" 13	95	22	—	100	1297	37.8	3015	0	—	—	—	—	
" 14	95	22	—	100	1297	37.5	2998	0	—	—	—	—	
" 15	—	—	—	100	700	38.0	3350	0	—	—	—	—	

TABLE II.

Case No. 75.

Date.	Weight	Diet.					Urine.				Blood Plasma.		
		Alcohol.	Carbohydrate.	Protein.	Fat.	Calories.	Volume.	Sugar.	Total Acetone bodies.	Total N.	Sugar mg. per 100cc.	Co2 Vol. %	Total Acetone bodies mg. per 100cc.
1917	Kg.	gm.	gm.	gm.	gm.		c.c.	gm.	gm.	gm.			
July 16	37.2	100	—	95	25	1315	3205	neg.	neg.	—	—	—	—
" 17	38.3	100	—	95	25	1315	3420	"	"	—	—	—	—
" 18	38.2	100	—	95	25	1315	3808	"	"	—	—	—	—
" 19	38.4	100	—	95	25	1315	4510	"	"	—	—	—	—
" 20	38.0	100	—	95	25	1315	4595	"	"	—	—	—	—
" 21	37.0	100	Fast-Day			700	2810	"	"	—	—	—	—
" 22	36.9	100	—	65	19	1144	2990	"	"	—	—	—	—
" 23	37.1	125	—	95	25	1490	3795	"	0.34	20.39	—	—	—
" 24	36.8	150	—	95	25	1665	4628	"	0.42	15.27	—	—	—
" 25	37.1	200	—	95	25	2105	3775	"	0.68	16.61	—	—	—
" 26	37.0	225	—	95	25	2190	4020	"	1.29	17.52	—	—	—
" 27	37.1	250	—	95	25	2365	4175	"	1.54	15.35	—	—	—
" 28	37.0	261	—	95	25	2443	3935	"	1.08	12.19	122	58.9	29.0
" 29	36.8	200	Fast-Day			1400	1340	"	0.54	12.19	132	66.3	28.4
" 30	35.6	200	—	95	151	3189	2155	"	1.53	15.09	161	69.3	27.1
" 31	36.7	200	—	95	151	3189	2155	"	2.61	11.62	—	—	—
Aug. 1	36.0	200	—	95	151	3189	2700	"	3.32	11.82	—	—	—
" 2	36.5	200	—	95	151	3189	3585	"	5.63	13.62	—	—	—
" 3	37.0	200	—	95	151	3189	4080	"	3.62	13.06	—	—	—
" 4	37.0	200	—	95	151	3189	5708	"	2.30	10.54	159	—	46.0
" 5	37.0	200	Fast-Day			1400	1220	Faint	0.78	7.69	149	72.1	35.4
" 6	35.5	200	—	95	151	3189	3675	neg.	2.09	15.84	141	79.6	36.8
" 7	37.2	200	—	95	151	3189	4605	"	6.03	14.28	—	—	—
" 8	38.2	200	—	95	151	3189	4005	"	4.60	11.70	—	—	—
" 9	38.0	200	—	95	151	3189	3975	"	1.79	10.34	—	—	—
" 10	37.9	200	—	95	151	3189	4265	"	3.07	13.22	—	—	—
" 11	38.2	200	—	95	151	3189	4142	"	1.16	12.01	112 *	66.4	37.6
" 12	38.7	—	Fast-Day			2170	2170	Faint	1.31	9.11	212	—	26.8
" 13	37.8	—	—	95	151	1789	3605	"	2.53	12.98	192	72.1	31.3
" 14	38.8	—	—	95	151	1789	4579	22.90	2.54	13.28	—	—	—
" 15	—	—	—	95	151	1789	4680	21.99	1.40	15.91	—	—	—
" 16	38.3	178	—	95	16	1791	3415	14.00	0.85	17.08	151	67.3	44.2
" 17	38.4	178	—	95	16	1791	2945	14.73	0.62	14.14	—	—	—
" 18	38.6	153	—	95	16	1616	2825	51.98	0.88	11.87	—	—	—
" 19	—	153	Fast-Day			1071	2920	Faint	0.64	8.47	—	—	—
" 20	37.6	178	—	—	—	1246	2785	neg.	0.92	13.37	—	—	—
" 21	37.3	178	—	95	16	1791	4157	8.73	1.95	18.29	—	—	—
" 22	37.9	178	—	95	16	1791	4300	21.50	1.98	20.44	—	—	—
" 23	38.3	178	—	95	7	1701	3875	30.00	1.73	22.48	373	64.5	27.2
" 24	37.7	178	—	95	7	1701	3775	40.39	1.32	23.41	370	65.5	15.4
" 25	38.0	178	—	95	7	1701	4400	44.44	—	18.48	400	59.8	11.4
" 26	37.8	178	Fast-Day			1246	2225	neg.	0.22	8.68	344	59.8	2.5
" 27	36.9	178	—	—	—	1246	2295	"	1.26	11.93	—	—	—
" 28	36.6	50	—	50	4	587	3165	"	0.57	13.92	—	—	—

* At 4 p. m.

TABLE II.

(Continued).

Date.	Weight.	Diet.					Urine.				Blood Plasma.		
		Alcohol.	Carbohydrate.	Protein.	Fat.	Calories.	Volume.	Sugar.	Total Acetone bodies.	Total N.	Sugar mg. per 100cc.	Co2 Vol. %	Total Acetone bodies (mg. per 100cc.)
1917	Kg.	gm.	gm.	gm.	gm.		cc.	gm.	gm.	gm.			
Aug. 29	36.8	50	—	50	4	587	3510	neg.	0.74	14.74	—	—	—
" 30	37.2	50	—	50	4	587	2835	"	0.71	11.63	—	—	—
" 31	37.3	50	—	50	4	587	3530	"	0.35	13.77	—	—	—
Sept. 1	37.7	100	Fast-Day			700	3650	"	Faint	9.49	278	—	—
" 2	38.3	50	—	50	27	820	2910	"	0.18	11.06	159	7.10	Faint
" 3	38.0	50	—	50	27	820	3117	"	0.13	14.03	—	—	—
" 4	38.0	50	—	50	27	820	3770	"	0.45	9.80	—	—	—
" 5	38.8	50	—	50	27	820	3615	"	0.51	10.45	—	—	—
" 6	39.2	50	—	50	27	820	3885	"	0.26	13.21	—	—	—
" 7	38.4	50	—	50	27	820	3228	"	0.52	10.98	—	—	—
" 8	38.6	50	—	50	27	820	4285	"	0.26	9.86	—	—	—
" 9	37.6	100	Fast-Day			700	2295	"	0.53	10.70	218	67.1	44.0
" 10	38.8	50	—	50	27	820	4150	"	—	—	156	68.1	28.0

Patient No. 75²⁸, male, unmarried, age 33, was admitted to the Hospital on Feb. 21, 1917, with severe diabetes of nearly 3 years' known duration. After cessation of glycosuria and approximate determination of the tolerance, he was subjected first to tests with high fat diets, as shown in Table IX of the former publication, which is here reproduced. Table II, which follows, gives the results of the ensuing alcohol experiment. The results of the fat test are thus summarized in the publication mentioned (pp. 518-522).

"This patient had been kept in the hospital from February 21, 1917, on diets up to 60 gm. protein and 1850 calories, with urine very commonly showing the faintest detectable traces of sugar and ferric chloride reactions, but never titratable quantities of sugar in the two month period. In correspondence with the urine, the blood showed continuous hyperglycemia and a moderate increase of total acetone (31 mg. per 100 cc.) at the time the test was made. A week before this (April 30) the protein had been increased by 10 gm., and the diet at the beginning of the test consisted of 70 gm. protein and 1500 calories. In addition there was an allowance of 600 cc. clear soup and 800 gm. thrice cooked vegetables daily, which were ignored in reckoning food values. With the increase in protein, sugar reactions became slightly more pronounced in the urine, but no titratable quantity was excreted. Under these conditions 100 gm. fat was added to the diet on May 21 and another 50 gm. on May 22, so that the diet May 22 to 30 consisted of 70 gm. protein, 281 gm. fat, and 2895 calories. Also 100 gm. olive oil

was given on the fast-day of May 27. The result, as seen in the table and the graphic chart, was a prompt glycosuria and ketonuria of considerable degree, also a rise of sugar and still more marked rise of acetone bodies in the blood, with a tendency to lowering of the bicarbonate reserve. Notwithstanding the giving of 100 gm. olive oil on May 27, this fast-day accomplished part of the usual purpose. There was no reduction of blood sugar. The blood taken at 10 A.M. on May 27, before the oil had been given, showed the benefit of abstinence up to that point in a lowering of total acetone and a rise in the CO₂ capacity. The 100 gm. oil was then given, and as this was so much less than the fat of the regular diet, this day of undernutrition apparently accomplished part of the benefit of a fast-day in checking the rise of acetone and fall of CO₂ capacity. The giving of 20 gm. sodium bicarbonate on May 28, 29, and 30 lowered the blood sugar only transiently if at all. It evidently safeguarded the plasma bicarbonate, but either failed to prevent the marked increase in plasma acetone, or possibly contributed directly to this increase. On May 30 the total acetone had reached the dangerous level of 108 mg. per 100 cc., and the patient's clinical condition was so unfavorable that prudence demanded a change in the diet. There was none of the dyspnea characteristic of acid poisoning, but intoxication was manifested by dizziness, malaise, weakness, and drowsiness. Beginning May 31, fat was excluded from the diet as far as convenient, keeping the protein ration unchanged. The table shows how in the remaining 3 days of that week all symptoms except the hyperglycemia strikingly improved. The clinical transformation was equally plain. Traces of glycosuria persisted up to June 13. Beginning June 18, the very low ration was augmented by first 70 gm. and then 100 gm. alcohol, but the total calories never exceeded 1300. Under this program, not only was there cessation of glycosuria and of ketonuria (aside from the trace indicated by a slight nitroprusside reaction), but also by July 1 the blood was normal in sugar, acetone, and alkali reserve. As an additional test of the relative importance of protein in producing the former glycosuria, a gradual increase of protein was then made, and it was found that with as much as 95 gm. protein and 1300 calories glycosuria was still absent on July 14."

This patient was thoroughly habituated to alcohol, and took the two-hourly doses of whiskey without difficulty and with pleasure. Up to July 24, the total calories were kept within the established tolerance of about 1500, and the clinical and chemical conditions remained excellent. An increase was then made, up to a maximum of 261 gm. alcohol and 2443 calories on July 28. The blood sugar showed no elevation in consequence of these few days of excess diet, again confirming the absence of any direct conversion of alcohol into sugar. Ketones, however, appeared in the blood and urine in small but distinct quantities.

Keeping the alcohol intake at the high level of 200 gm. daily, the former fat ration of 25 gm. was raised to 151 gm. daily, with a view to comparing the results of an excess diet of mixed fat and alcohol with the previous excess of fat alone. As usual with increase of foods

which are not directly transformed into sugar, the effects were slow in appearing, but by Aug. 12 the plasma sugar had risen to 0.212%. As usual also, these effects which are slow in appearing are slow in ceasing, and heavy glycosuria occurred during the ensuing week notwithstanding a considerable reduction in calories.

This reduction was accomplished by omitting alcohol altogether for 4 days. The first of these was the routine fast-day, but on the remaining 3 (Aug. 13-15) the diet otherwise was kept unchanged, consisting of 1789 calories of protein and fat. The fat was then reduced as low as feasible, and 178 gm. of alcohol given daily, so as to maintain (aside from minor accidental variations) the same energy value of approximately 1791 calories up to Aug. 25. No appreciable difference was seen between fat and alcohol. The glycosuria, which began in the fat period, continued and even increased in the alcohol period. It was checked by the fast-days (with alcohol) of Aug. 19, 20, 26 and 27, but a sharp reduction of the total diet was necessary to retrieve the damage done. By the usual regulation of total diet the blood and urine were then brought to normal and kept so continuously until the patient's discharge from hospital in May 1918. He was stronger and more comfortable clinically in this condition on lower diets than with the active diabetic symptoms brought on by the attempts at excessive feeding.

The remarks on this experiment may be divided into those concerning protein, sugar and acetone.

1. *Protein.* — As in the preceding case, no nitrogen balances were determined. The soup, being thin, probably did not add greatly to the nitrogen output. It is evident from the urinary nitrogen that an appreciable nitrogen storage was effected during the period of highest caloric diets. A comparison of the period Aug. 12-15 (without alcohol) with the ensuing period up to Aug. 26 (with alcohol substituted for fat) shows that the nitrogen output was appreciably higher in the latter period, giving the impression that alcohol was distinctly inferior to fat in sparing protein.

The ration of 95 gm. protein began on July 11, and the first significant rise of blood sugar was found on Aug. 12. The preliminary period in this case was therefore ample to dispose of any supposition that the observed results were due to protein alone. In fact, general experience indicates that hyperglycemia due solely to a sugar-forming food such as protein occurs promptly enough that the length of the preliminary period in case No. 43 was really sufficient.

Sugar. — This experiment affords three indications that alcohol is not converted into sugar in the body.

(a) In the period from June 18 to July 28, the daily addition of alcohol to the diet in quantities increasing from 70 to 261 gm. occasioned neither glycosuria nor hyperglycemia in this severe case of diabetes.

(b) Though there was thus no perceptible impairment of carbohydrate assimilation, an appreciable increase of ketones in blood and urine appeared during this period, while a diminution should have been expected from a sugar-forming food.

(c) It is known from the literature that the respiratory quotient following alcohol ingestion is low, though the results in diabetic patients may sometimes be atypical²⁹. As carbohydrate, when freely available, takes precedence over fat in combustion, so alcohol apparently takes precedence, at least to a large extent, over all other foods and thus depresses the respiratory quotient even in the presence of carbohydrate. This may be a theoretical explanation of a phenomenon which was observed several times in these two patients and one other, namely the apparent temporary lowering of the blood sugar by alcohol. An extreme instance was given on Aug. 11, when the plasma sugar was 0.112% at 4 p. m., as compared with 0.212% on the following morning before any of the day's doses of alcohol had been taken. Also on Aug. 23, 24 and 25 observations were made as shown in Table III.

TABLE III. *

Influence of Alcohol on Blood Sugar and Acetone.

Date.	Hour.	Plasma Sugar mg. per 100cc.	Co2 vol. %	Qual. Acetone.	Acetone- Diabetic acid, mg. per 100cc.	B-Oxy- butyric acid, mg. per 100cc.	Total Acetone mg. per 100cc.
August 23	9:00	373	64.5	0	4.8	22.4	27.2
" "	10:00	370	41.9	0	trace.	20.2	20.2
" "	11:00	322	43.9	0	"	18.7	18.7
" "	5:00	256	60.7	0	—	—	—
" 24	8:45	370	65.5	0	trace.	15.4	15.4
" "	9:45	345	64.5	0	"	19.6	19.6
" "	10:45	312	60.7	0	"	10.7	10.7
" "	5:00	286	54.1	0	"	19.6	19.6
" 25	9:30	400	59.8	0	"	11.4	11.4
" "	10:45	384	48.5	0	"	16.4	16.4
" "	11:45	344	60.7	0	0	20.4	20.4
" "	5:00	278	53.8	0	0	11.5	11.5

* For urinalyses for these days, see Table II.

It is believed that the marked fall in plasma sugar during these three days can be attributed only to the alcohol. Though the point has not been sufficiently studied to warrant a definite judgment, it seems interesting enough that it would have been pursued further had circumstances permitted. One question still deserving investigation is whether alcohol may sometimes actually depress glycosuria temporarily, as reported by authors. If so, its reported antiketogenic action in such cases may be explained.

Granting that alcohol is not converted into sugar and that it may possibly lower the blood sugar temporarily, the final effect of the prolonged *luxus* rations of mixed fat and alcohol was marked hyperglycemia and glycosuria. This cumulative action was not halted by the withdrawal of either alcohol or fat from Aug. 11 to 26, partly because the damage to the assimilative power is actually cumulative, and partly because this reduced diet of about 1790 calories was still in excess of the known tolerance of the patient.

3. *Acetone*. — As mentioned above, alcohol apparently produced a slight increase of acetone in blood and urine when the dosage became sufficiently high, even in the absence of any demonstrable disturbance of carbohydrate metabolism. It thus cannot be credited with reducing ketone formation.

With the subsequent excessive rations of mixed alcohol and fat, maximum acetone figures of 5.6 gm. in the urine and 46 mg. per 100 cc. in the blood were obtained. The lowering of the CO_2 capacity of the plasma to 41.9 and 43.9 volume per cent. on Aug. 23 and to 48.5% on Aug. 25 seems to require some other explanation than the small quantities of acetone then present. (Table III.) Whether a special effect of alcohol on respiration or tissue exchanges was responsible is uncertain.

The contrast in acidosis, however, both chemically and clinically, between these mixed alcohol-fat diets and the preceding experiment with fat alone in this patient is very striking. With the excessive increase of fat alone, the ketosis was increased in parallel, till it reached dangerous proportions. With the later alcohol-fat ration, the fat component was not extremely high and the acidosis was accordingly moderate. Therefore, if alcohol is not anti-ketogenic, the experiment confirms the view that it is not convertible into acetone. It also indicates that if *luxus* diets are to be used in diabetes,

a mixture of fat and alcohol is safer than the caloric equivalent of pure fat from the standpoint of acidosis, and to this extent the former clinical use of alcohol in diabetes is justified.

CONCLUSIONS.

1. The experiments upon these two patients with severe diabetes support the prevailing belief that ethyl alcohol is not converted into sugar in the body. At the same time, they are interpreted as signifying that the addition of calories in the form of alcohol in excess of the patient's caloric tolerance produces a return of glycosuria and other diabetic symptoms.

2. The experiments also corroborate the prevailing view that alcohol is not converted into acetone in the body. No antiketogenic action was demonstrable; on the contrary a slight production of acetone seemed to be caused when alcohol was given in considerable quantities. *Luxus* diets formed by the addition of alcohol or a mixture of fat and alcohol to a standard diet gave rise to very much less acidosis both chemically and clinically than similarly excessive diets built up by the addition of fat alone. The former therapeutic use of alcohol is thus justified, with respect to the lessened danger of acidosis when part of the fat of a high caloric diet is substituted by alcohol. The experiments do not establish such a fact for undernutrition diets, or warrant attempts to prevent combustion of body fat by administration of alcohol. On the contrary, the conversion of an undernutrition diet into a *luxus* diet by addition of alcohol may result in an actual increase of acetone. No experiments with coma were performed, and conclusive tests here would be difficult to devise, but the above facts agree with the prevailing clinical practice which has abandoned the use of alcohol in the treatment of coma.

3. With additions of alcohol, just as with additions of fat, the high caloric rations which were hoped to increase the weight and strength of emaciated patients failed to do so. As usual, the patients were stronger and more comfortable on diets which controlled their diabetes than on higher allowances which produced a return of diabetic symptoms.

4. The experiments with alcohol, if fully confirmed, are of crucial importance in supporting the undernutrition treatment. They add to the existing evidence that the assimilative

power of the diabetic organism is limited not only in respect to carbohydrate (preformed or potential) but also in respect to total calories as such; in other words that the very nature of diabetes consists in inability to assimilate more than a certain total diet or carry more than a certain body weight, both of which are limited in proportion to the severity of the diabetes. In confirmation of the view that the harmfulness of excessive fat in diabetes does not consist merely in its possible conversion into either sugar or acetone but preeminently in the overload of the total metabolism, it is found that alcohol, which is clearly recognized as not convertible into sugar or acetone in the body, produces a return of glycosuria and other symptoms when added to the diabetic diet in quantities exceeding the caloric tolerance. One incidental deduction from this fact is the difference between the specific metabolic defect which constitutes diabetes, and any non-diabetic form of glycosuria superficially imitating it, such as phlorizin poisoning. The most important lesson, however, is that all attempts to find some special or synthetic food which the diabetic shall be able to metabolize, so as to restore normal nutrition without excretion of sugar or acetone, are forever impossible³⁰. The endeavor to strengthen or fatten the diabetic individual with any kind of food in excess of his caloric tolerance entails an inevitably fatal result. This limitation of total assimilation and body weight cannot be circumvented, and can only be removed by a cure which shall supply the missing product of the pancreas.

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OVERNUTRITION WITH FAT AND ALCOHOL IN SEVERE DIABETES

By FREDERIC S. LECLERCQ

From The Physiatrie Institute, Morristown, New Jersey.

The writer formerly¹, alone and in collaboration with Kolisch, studied the influence of various substitutions in the diabetic diet upon the excretion of sugar and acetone. Since then, this subject has been enriched with new knowledge and improved methods. In the latest publication of Kolisch², he appears to be unaware that the plan of treatment which has been developed in America is the logical development of his own recommendations for the use of green vegetables and a fairly low calory diet, in which points he followed Bouchardat and opposed the excessive protein-fat rations employed by others.

The present research was undertaken to test the effect of added calories in the form of fat or alcohol upon the assimilative capacity of diabetic patients. The particular point in view was to determine whether such patients are limited in their tolerance for total calories, as indicated by a return of diabetic symptoms upon attempting to add calories in excess of this limit or build up a higher body weight, even though the intake of protein and carbohydrate is kept constant at quantities previously tolerated. In order to settle this point in reasonably short tests, it is necessary to choose patients with sufficiently severe diabetes, who will show the effects of such a dietary change more quickly than milder cases, and also those who have been under exact observation for a sufficiently long time to establish that the alterations in question are not accidental fluctuations.

For this test, therefore, were selected two patients who have lived continuously in the Physiatrie Institute for approximately two years, because of their inability to control their severe diabetes successfully at home. Patient No. 24, male, aged 29 years, has had diabetes for over 8 years, and in ad-

dition has nephritis with a tendency to nitrogen retention to such extent that his blood urea has at times been over 200 mg. per 100 cc. on low protein diets. His height is 5 feet 6 inches. His highest weight was 142 pounds before diabetes. In the Institute he has maintained equilibrium of weight and nitrogen (apart from occasional edema) at a weight of about 80 pounds, on a diet of 50 gm. protein, 15 gm. carbohydrate and 1000 calories.

Patient No. 85, male, aged 33 years, has had diabetes for nearly 7 years, and is otherwise normal except for susceptibility to diabetic edema. His height is 5 feet 9 $\frac{3}{4}$ inches. His normal weight was 165 pounds. In this Institute he has been in equilibrium at a weight of about 100 pounds, on a diet of 55 to 60 gm. carbohydrate and 1100 to 1200 calories.

Both patients are ambulant and occupied with very light duties every day. Their histories will be given in a subsequent paper, to which reference may be made for details. Their tolerance seems to be stationary, and their urine and blood sugar have been kept normal except for occasions when attempts have been made to improve their weight or strength by additions to their diet. The present experiments consisted in observing the effects of added calories in the form of fat or alcohol respectively. Soup and other disturbing factors were withdrawn from the diet 10 days before beginning the tests. The diets were not analyzed, but were calculated from food tables as usual, and consisted also of practically the same foods in the different periods. Nine small bran biscuits per day were the only things taken for which no food value was counted. Benedict's method was used for sugar, the urease method for urea, and the common laboratory procedures for other analyses. All blood samples in Tables I and II were taken in the morning before ingestion of any food.

REMARKS ON TABLE I.

The diet for the fore-period, Oct. 3 to 23, was 50 gm. protein, 15 gm. carbohydrate and 1000 calories, with a weekly fast-day of only 10 gm. carbohydrate.

October 24 to 26 inclusive, the protein was reduced to 40 gm. and the carbohydrate to 5 gm. Adopting the calculation proposed by Woodyatt³, the 10 gm. protein thus subtracted was

TABLE I.
Case No. 24.

Date, 1921	Weight, lb.	DIET					BLOOD			URINE				Nitrogen balance	
		Protein gm.	Fat gm.	CH gm.	Alcohol gm.	Calories	Sugar mg. per 100 cc.	Urea mgm. per 100 cc.	Uremia Qual.	Volume cc.	Sugar Qual.	Nitro prusside reaction	Total N gm.	Grams daily	Average gm.
Oct. 3	84	50	82	15		1000				1830	0	0	9.05	+1.71	
4		50	82	15		1000	150			2140	0	0	7.18	-0.16	
5	83	50	82	15		1000				2430	0	0	11.50	-4.17	
6		50	82	15		1000				2010	0	0	5.44	-1.86	
7	82	50	82	15		1000	129	74		1840	0	0	7.93	-0.59	
8		50	82	15		1000				1730	0	0	5.74	+1.60	
9	83			10		40				1900	0	0	6.12	-6.12	
10		50	82	15		1000				1710	0	0	7.42	-0.08	
11	82	50	82	15		1000	117	-		2260	0	0	7.56	-0.12	
12		50	82	15		1000				3080	0	0	8.35	-1.01	
13	82	50	82	15		1000				2310	0	0	9.70	-2.36	
14		50	82	15		1000	133	-		1830	0	0	8.45	-1.11	
15		50	82	15		1000				1780	0	0	6.99	+0.35	
16		-	-	10		40				800	0	0	5.11	-5.11	
17		50	82	15		1000				1835	0	0	9.19	-1.86	
18	80	50	82	15		1000				2260	0	0	7.96	-0.62	
19		50	82	15		1000				2020	0	0	7.28	+0.06	
20	80	50	82	15		1000				1505	0	0	6.96	+0.38	
21		50	82	15		1000	137			1555	0	0	6.92	+0.42	
22		50	82	15		1000				1570	0	0	7.12	+0.22	
23		-	-	10		40				1290	0	0	5.70	-5.70	-1.30
24	76	40	240	5		2340				1820	0	0	8.91	-3.04	
25		40	240	5		2340	242	40		2205	0	0	7.84	-1.97	
26		40	240	5		2340	300	-	+++	2810	0	0	7.63	-1.56	-2.19
27		60	24	15		516	375	-	+++	2400	0	0	9.94	-1.14	
28		60	24	15		516	306	-	++	2170	0	0	8.99	-0.19	
29	76½	60	24	15		516				1760	0	0	8.57	+2.30	
30		-	-	10		40	184	-		1470	0	0	7.69	-7.69	
31		60	24	15		516				1730	0	0	3.90	+4.90	-0.36
Nov. 1	78	50	82	15		1000	102	102		2500	0	0	8.82	-1.48	
2		50	82	15		1000				2845	0	0	12.55	-5.21	
3	77½	50	82	15		1000				2300	0	0	10.40	-3.06	
4		50	82	15		1000	121	85		2390	0	0	10.10	-2.76	
5	76	50	82	15		1000				1665	0	0	7.78	-0.44	
6		-	-	10		40				1160	0	0	4.41	-4.41	
7	79	50	82	15		1000				1920	0	0	16.65	-9.31	
8		50	82	15		1000	93	-		1790	0	0	7.26	+0.08	
9	79	50	82	15		1000				1600	0	0	6.72	+0.62	
10		50	82	15		1000				1520	0	0	5.81	+1.54	
11	79	50	82	15		1000	152	-		1490	0	0	5.84	+1.50	
12		50	82	15		1000				1840	0	0	4.15	+3.19	-1.64
13	81	40	-	5		180				2120	0	0	4.74	+1.13	
14		50	82	15		1000				1785	0	0	7.92	-0.58	
15	83	50	82	15		1000	116	78		2370	0	0	7.96	-0.62	-0.02

TABLE 1. (Continuation).

Date, 1921	Weight, lb.	DIET					BLOOD			URINE				Nitrogen balance	
		Protein gm.	Fat, gm.	CH gm.	Alcohol gm.	Calories	Sugar mg. per 100 cc.	Urea mg. per 100 cc.	Libemia Qual.	Volume cc.	Sugar Qual.	Nitro prusside reaction	Total N gm.	Grams daily	Average gm.
Nov. 16	...	50	82	15	...	1000	2370	0	0	6.24	+1.10
17	80	50	82	15	...	1000	2700	0	0	10.58	-3.14
18	...	50	82	15	...	1000	171	...	++	2585	0	0	7.16	+0.18	-0.28
19	79	50	82	15	120	1840	2150	0	0	3.13	+4.21
20	...	40	-	5	120	1020	2400	0	+	11.50	-5.63
21	...	50	82	15	120	1840	2050	0	+	10.33	-1.99
22	79	50	82	15	120	1840	214	42	++	1960	0	0	10.10	-1.76
23	...	50	82	15	120	1840	1470	+	0	5.05	+2.29
24	...	60	-	25	120	1180	1440	+	+	5.04	+3.76
25	82	50	82	15	120	1840	270	...	+	1720	+	0	6.26	+1.08
26	...	50	82	15	120	1840	285	...	++	1490	+	0	4.62	+2.72	+0.59
27	83	40	-	5	...	180	1300	+	0	10.60	+5.73
28	...	50	82	15	...	1000	230	2010	+	0	8.80	-1.46
29	...	50	82	15	...	1000	2870	+	0	12.90	-5.56
30	83	50	82	15	...	1000	319	148	...	1950	+	0	8.40	-1.06
Dec. 1	...	50	82	15	...	1000	1746	+	0	7.50	-0.16
2	...	50	82	15	...	1000	312	46	...	1320	+	0	4.10	+3.24
3	78	50	82	15	...	1000	1870	+	0	7.80	-0.46
4	...	40	-	5	...	180	1590	0	0	6.80	-0.93
5	...	50	82	15	...	1000	187	47	...	1810	0	0	6.50	+0.84
6	...	50	82	15	...	1000	1800	0	0	3.90	+3.44
7	...	50	82	15	...	1000	2250	0	0	3.90	+3.44
8	...	50	82	15	...	1000	1710	0	0	4.60	+2.74
9	...	50	82	15	...	1000	1810	0	0	8.80	-1.46
10	...	50	82	15	...	1000	1280	0	0	5.20	+2.14	+0.75
11	80	40	-	5	...	180	295	-	...	1440	0	0	7.80	-1.93
12	...	25	-	5	...	120	1400	0	0	3.90	-0.23
13	...	44	17	10	...	370	150	84	...	1770	0	0	4.30	+2.15
14	...	30	14	5	...	270	1950	0	0	8.00	-3.60
15	77	35	48	5	...	600	2140	0	0	7.50	-2.36
16	...	45	88	5	...	1030	156	78	...	2340	0	0	7.10	-0.50
17	...	45	88	5	...	1030	1600	0	0	6.20	+0.40
18	...	40	68	5	...	1030	2005	0	0	8.60	-2.73
19	75	55	82	10	...	1000	1050	0	0	5.70	+2.37
20	...	58	82	10	...	1000	246	78	++	1245	0	0	6.40	+2.10
21	...	30	19	2	...	300	1470	0	0	8.60	-4.20
22	...	37	19	2	...	325	123	80	...	1440	0	0	7.90	-2.40	-0.91
23	...	30	24	3	...	350	153	90	...	1360	0	0	8.50	-4.10
24	...	30	24	-	...	340	143	92	...	1665	0	0	9.20	-4.80
25	...	35	48	5	...	600	1690	0	0	8.40	-3.27
26	...	35	48	5	...	600	184	106	++	1810	0	0	9.30	-4.13
27	...	35	48	3	...	590	-	0	0	-	-
28	...	35	48	3	...	590	1220	0	0	4.60	+0.30
29	...	45	50	5	...	650	119	82	...	1380	0	0	7.50	-0.90
30	...	40	52	5	...	670	1340	0	0	5.60	+0.27
31	...	45	50	5	...	650	1510	0	0	6.80	-0.20	-2.12

assigned the value of 5.8 gm. glucose, and, as the carbohydrate ration had been reduced by 10 gm., the entire change meant a subtraction of 15.8 gm. carbohydrate (glucose) from the former diet. Counting fat as being 10% carbohydrate (glycerol), it was possible to add 158 gm. of fat to the former diet in exchange for this subtraction of glucose. The original energy value of 1000 calories was thus raised to 2340 calories, while keeping the theoretical carbohydrate content unchanged. In other words, a low protein, low carbohydrate, high fat diet such as advocated by Newburgh and Marsh⁴ was thus created. The unusually rapid onset of hyperglycemia and lipemia shown in the table was apparently due to the exceptionally severe nature of this case and the high caloric overload inflicted.

Owing to the alarming hyperglycemia, the diet was changed on Oct. 27, by raising the protein to 60 gm. and the carbohydrate to 15 gm. daily. Counting the carbohydrate equivalent of the 20 gm. protein added as 11.6 gm., this, with the 10 gm. carbohydrate added, made an addition of 21.6 gm. of glucose, for which it was permissible to subtract 216 gm. of fat so as to keep the potential carbohydrate total unchanged. This change reduced the energy value of the diet to 516 calories. The plasma sugar rapidly fell, as usual in treatment by under-nutrition, and by Nov. 1 had returned to a normal level.

On Nov. 7 the original diet of 50 gm. protein, 15 gm. carbohydrate and 1000 calories was restored, with continuance of normal glycemia except for the elevation to 0.152% on Nov. 11. Beginning Nov. 13, the regular fast-day allowance was changed to 40 gm. protein (egg white) and 5 gm. carbohydrate (green vegetables) for the sake of the patient's comfort.

From Nov. 19 to 26 inclusive, the diet was increased by the addition of 120 gm. of alcohol daily, given in the form of 95 per cent. alcohol diluted with water. No change was made in the other foods, as alcohol is not considered to be convertible into either sugar or acetone in the body. As the alcohol was distributed in small 2-hourly doses, no toxic symptoms were produced. The rise in the plasma sugar is evident from the table. Slight glycosuria also was present on 3 days. Probably because of the long period of caloric excess, the effects did not subside on withdrawal of the alcohol, and a temporary cut in diet was finally necessary to retrieve the damage to

the assimilation. It was subsequently possible to build up the diet to the previous level, on which the patient has since remained with continuously normal blood sugars as before.

REMARKS ON TABLE II.

The fore-period began Oct. 18, on the regular diet of 55 gm. protein, 10 gm. carbohydrate and 1100 calories, with a weekly day of partial fasting on 40 gm. protein (meat) and 5 gm. carbohydrate (green vegetables).

Oct. 24 to 27 inclusive, the protein was reduced to 40 gm. and the carbohydrate to 5 gm. daily. Counting the carbohydrate of protein as 58%, the reduction by 15 gm. of protein was equivalent to a subtraction of 8.7 gm. glucose, which, with the 5 gm. reduction of carbohydrate, equalled a total subtraction of 13.7 gm. glucose. Counting fat as 10% carbohydrate (glycerol), it was permissible to add 137 gm. fat to the former diet, thus making 230 gm. fat and 2250 total calories, while keeping the carbohydrate value of the original diet unchanged. Owing to the severity of the case, a very rapid rise of plasma sugar resulted, as shown in the table.

On Oct. 28 and 29, the protein was raised to 58 gm. and the carbohydrate to 15 gm. daily. Calculating the equivalent in fat, according to the theoretical formula, it was necessary to subtract 204.4 gm. of fat in order to keep the carbohydrate value of the diet unchanged. This left 25.6 gm. of fat and 522 total calories daily. This being a ration of marked undernutrition, the plasma sugar fell rapidly. On Oct. 31 the original diet of 55 gm. protein, 10 gm. carbohydrate and 1100 calories was resumed, and the plasma sugar remained within low normal limits.

Nov. 18 to Dec. 3, alcohol was added to the diet (100 gm. daily on the first two days, 120 gm. daily thereafter), thus raising the total calories first to 1800 and then to 1940. Hyperglycemia and slight glycosuria resulted. Owing to the length of this overnutrition period, the damage to the assimilation was not removed by the simple withdrawal of alcohol. For fear of permanent injury to the tolerance, it was necessary after Dec. 13 to make a general reduction of the diet, which only slowly brought the plasma sugar again to normal, as shown in the table. Subsequently the diet was gradually built

TABLE II.
Case No. 85.

Date, 1921	Weight, lb.	DIET					BLOOD			URINE				Nitrogen balance	
		Protein gm.	Fat, gm.	CH gm.	Alcohol gm.	Calories	Sugar mg. per 100 cc.	Urea mg. per 100 cc.	Lipemia Qual.	Volume cc.	Sugar Qual.	Nitro prusside reaction	Total-N gm.	Grams daily	Average gm.
Oct 18	104	55	93	10	—	1100	93			2500	0	0	9.5	-1.43
19	...	55	93	10	—	1100				4200	0	0	6.4	+1.67
20	...	55	93	10	—	1100				2845	0	0	6.1	+1.97
21	107	55	93	10	—	1100				2980	0	0	5.5	+2.49
22	...	55	93	10	—	1100				3500	0	0	5.8	+2.27
23	...	40	25	5	—	405				2205	0	0	3.4	+2.50	+1.58
24	...	40	230	5	—	2250				1610	0	0	7.9	-2.03
25	101	40	230	5	—	2250	159			3205	0	0	6.1	-0.23
26	...	40	230	5	—	2250	214		++	4050	0	+	5.9	-0.03
27	100	40	230	5	—	2250	260		+++	2290	0	+	5.5	-0.37	-0.48
28	...	58	25	15	—	520	230		++	3600	0	+	7.3	+1.22
29	...	58	25	15	—	520				2300	0	+	7.3	+1.22	+1.22
30	...	40	25	5	—	405	162			1210	0	+	6.7	-0.80
31	...	55	93	10	—	1100				1790	0	+	9.2	-1.13
Nov 1	98	55	93	10	—	1100	75			2290	0	0	14.6	-6.53
2	...	55	93	10	—	1100				1760	0	0	11.7	-3.63
3	...	55	93	10	—	1100				2716	0	0	12.1	-4.03
4	...	55	93	10	—	1100	100			3410	0	0	8.9	-0.83
5	...	55	93	10	—	1100				3160	0	0	7.3	+0.77	-2.10
6	...	40	25	5	—	405				2395	0	0	6.8	-2.90
7	100	55	93	10	—	1100				1855	0	0	9.5	-1.43
8	...	55	93	10	—	1100	79	8		2665	0	0	10.4	-2.33
9	102	55	93	10	—	1100				3450	0	0	8.1	-0.03
10	...	55	93	10	—	1100				2540	0	0	7.1	+0.97
11	...	55	93	10	—	1100	125	15		2560	0	0	4.3	+3.77
12	...	55	93	10	—	1100				3320	0	0	6.9	+1.17	-0.11
13	106	40	25	5	—	405				2900	0	0	6.3	-0.43
14	...	55	93	10	—	1100				2640	0	0	8.2	-0.13
15	105	55	93	10	—	1100	100			2260	0	0	7.9	+0.17
16	...	55	93	10	—	1100				1550	0	0	3.6	+4.47
17	110	55	93	10	—	1100				2560	0	0	9.0	-0.93	+0.61
18	...	55	93	10	100	1800				4160	0	0	8.2	-0.13
19	109	55	93	10	100	1800				2620	0	0	12.7	-4.63
20	...	40	25	5	120	1245				680	0	0	8.5	-2.63
21	105	55	93	10	120	1940				3520	0	0	9.0	-0.93
22	...	55	93	10	120	1940	178			1870	0	0	6.0	+2.07
23	107	55	93	10	120	1940				3050	0	0	7.0	+1.13
24	...	55	93	10	120	1940	260			2860	0	0	6.2	+2.58
25	...	55	93	10	120	1940				1830	0	0	3.6	+4.47
26	...	58	93	10	120	1940				2030	0	0	5.4	+2.67
27	110	40	25	5	120	1245	214			3110	0	+	6.2	-0.33
28	...	55	93	10	120	1940				2430	0	—	7.6	+0.47
29	110	55	93	10	120	1940	182			1830	0	+	4.6	+3.47	+0.63

TABLE II. (*Continuation*).

Date, 1921	Weight, lb.	DIET					BLOOD			URINE				Nitrogen balance	
		Protein gm.	Fat, gm.	CH gm.	Alcohol gm.	Calories	Sugar mg. per 100 cc.	Urea mg. per 100 cc.	Liponita Quat.	Volume cc.	Sugar Qual.	Nitro prusside reaction	Total-N gm.	Grains daily	Average gm.
Nov. 30	55	93	10	120	1940	3830	0	+	6.6	+1.47
Dec. 1	55	93	10	120	1940	3680	0	+	7.9	+0.17
2	55	93	10	120	1940	226	8	2810	0	+	7.8	+0.27
3	100	55	93	10	120	1940	2520	+	0	5.9	+0.17	+0.64
4	40	25	5	—	405	230	15	3350	0	0	9.0	-3.13
5	55	93	10	—	1100	2270	0	0	8.7	-0.63
6	98	55	93	10	—	1100	199	24	2780	0	0	9.6	-1.53
7	55	93	10	—	1100	2860	0	0	8.7	-0.63
8	98	55	93	10	—	1100	3540	0	0	8.3	-0.23
9	55	93	10	—	1100	242	3460	0	0	8.2	-0.13
10	100	55	93	10	—	1100	3060	0	0	9.5	-1.43	-1.10
11	40	25	5	—	405	3580	0	0	9.5	-3.63
12	55	93	10	—	1100	2980	0	0	10.6	-2.53
13	55	93	10	—	1100	203	3460	0	0	9.5	-1.43
14	100	30	20	5	—	320	2530	0	0	8.1	-3.70
15	35	48	5	—	600	2960	0	0	8.0	-2.86
16	101	35	48	5	—	600	157	2770	0	0	9.1	-3.96
17	101	35	48	5	—	600	2510	0	0	9.3	-4.16	-3.18
18	103	30	—	1	—	1 25	2250	0	0	11.6	-7.2
19	103	45	77	5	—	900	119	2660	0	0	10.3	-3.7
20	104	45	77	5	—	900	2800	0	0	8.2	-1.6
21	45	77	5	—	900	178	28	3450	0	0	7.7	-1.1
22	105	40	45	2	—	575	2070	0	0	10.1	-4.23
23	40	45	2	—	575	2495	0	0	6.6	-0.73
24	35	44	2	—	540	2490	0	0	5.7	-1.56	-2.87
25	35	49	4	—	600	101	2655	0	0	6.8	-1.66
26	104	35	49	4	—	600	2105	0	0	6.4	-1.26	-1.46
27	35	49	4	—	600	100

up to the original level, on which the patient has maintained normal blood sugar concentrations to the present.

DISCUSSION OF RESULTS.

Nitrogen balance.—The ability of these two patients to maintain a level of weight and strength during two years indicated that they were in nitrogen equilibrium. The nitrogen balances shown are not to be considered exact, as only the urinary nitrogen was analyzed. The diets were calculated from food tables as usual in the diet kitchen, and the fecal nitrogen

was merely estimated roughly as one-twelfth of the food nitrogen. The tendency to slightly negative balances, however, led to an investigation which proved to be of practical value. Most of the foods were weighed raw, but for some meals some meats, especially roasts, were permitted to be weighed after cooking and calculated according to tables for cooked meats. It was found that through cooking these too dry, to please the patients, the protein values had been made considerably too high, as will be reported later by Dr. L. S. Fuller. The apparent negative balances were thus explained by the fact that the intake was actually a little higher than calculated, but as the portion of protein weighed in the cooked form was small and as the succession of menus was practically the same throughout the entire experiment, no essential disturbance of the results is created for comparative purposes. As far as the figures have absolute value, they confirm the results of Mosenthal and Harropp.

The one important purpose in analyzing the urinary nitrogen and calculating the approximate nitrogen balance was to rule out any source of error, due to the possibility that the amount of protein actually catabolized might differ appreciably from the amount ingested. The data suffice to exclude accusations of error based on such an assumption. On the contrary, the addition of surplus calories must serve to prevent catabolism of body fat and protein, and this was the time when the plasma sugar readings rose. Undernutrition tends to the breaking down of body fat and protein in addition to that calculated in the diet, and the usual therapeutic benefit of undernutrition was evident nevertheless.

Occasional irregularities in the daily nitrogen output, particularly low values on a few days, are probably explainable by retention, as one patient had nephritis and the other was subject to edema. The higher blood urea figures with alcohol suggested injury of the renal function in the nephritic patient No. 24, but no such urea retention occurred with alcohol in patient No. 85.

Clinical results.—In no instance was a gain of weight and strength or other clinical benefit accomplished. Both patients were stronger and better satisfied for the first few days, but quickly began to complain of discomfort and weakness. Such a

^{distant} distant also developed for both fat and alcohol that neither type of diet could have been continued for any great time longer, even if clinically desirable. The undernutrition necessary to undo the harm of the excessive diets negated any nutritive benefit from them.

Effect on assimilation.—The effect of adding excess calories of either fat or alcohol was an injury of assimilation. As this injury occurred from fat, when an increase of the theoretical glucose value of the diet by reason of the glycerol of the fat was avoided, and also occurred from alcohol, which is not convertible into either glucose or acetone in the body, it is inferred that the harm was due to the excess of calories as such. This harm was judged generally by the hyperglycemia produced. At most, no more than traces of sugar were allowed to appear in the urine. Allen has shown that such harm can be carried to the point of heavy glycosuria and acidosis in suitable prolonged experiments, but there was fear of permanent lowering of the tolerance if such experiments should be thus prolonged in such severe cases. It should be repeated that the great rapidity of the manifestation of injury from fat or alcohol in these cases is unusual, and in the great majority of cases a longer time, sometimes several weeks, is required for such results. The very quick and striking effect in these two cases is believed to be due to their very severe character, which entails the greatest sensitiveness to any dietary excess.

Principle of limitation of calories in treatment.—The principle illustrated in these experiments serves to explain the benefits gained by fasting and undernutrition and also by regulation of the total calories in the subsequent treatment. As use was made of Woodyatt's calculations for the diet, it should be pointed out that no necessary antagonism exists with reference to Woodyatt's work. The latter deals only with possible substitutions between food substances on the basis of their glucose or fatty acid values, and imposes no choice as to whether high or low calories should be used in treatment. Low diets can be calculated on Woodyatt's plan as easily as high diets. Woodyatt's recommendation of a balance between glucose and fatty acids in the diet is also similar to that in the diets found beneficial here and opposed to the

excessive fat diets which were found harmful. A dispute, therefore, exists only with those persons who deny the need of caloric restriction or defend the old-fashioned high-calory diets. With reference to the views of Newburgh and Marsh, likewise, a difference of opinion can arise only if their fat-rich diets are pushed to a point exceeding the caloric tolerance of any patient. It may be repeated that this paper does not concern the balance of foodstuffs in the diet, but the findings merely support the principle of total caloric restriction in diabetes.

CONCLUSION.

These experiments on two patients with severe diabetes demonstrate the production of hyperglycemia in consequence of adding excessive calories to the diet in the form of either fat or alcohol. They thus confirm the harmful results previously described by Allen, to whom the writer expresses thanks for advice and assistance in this problem.

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ON THE RELATIONS BETWEEN FERTILITY AND NUTRITION *

I. THE OVULATION RHYTHM IN THE RAT ON A STANDARD NUTRITIONAL REGIME.

BY HERBERT M. EVANS AND KATHERINE S. BISHOP

Department of Anatomy, University of California.

(Received for publication Feb. 8, 1922.)

The determination by Long and Evans of the microscopic criteria for the detection of oestrus in the rat — the classical animal for nutrition studies — enables us for the first time to study the nutritive relations of the physiology of the gonads, for the studies to which we refer have also shown that oestrus is related to ovarian activity and is normally associated in a definite way with ovulation. We may now investigate not merely general growth or the maintenance of body weight in animals but a particular physiological mechanism which regularly within cycles of four or five days imposes a series of changes upon the organs of reproduction — changes which are associated with cyclic development and rupture of graafian follicles and the discharge of eggs from the ovary. It is conceivable that certain nutritive regimes may permit growth to occur and yet may prevent or interfere with this cyclic ovulatory mechanism. We hope to show that this is the case. And yet a broader view of the advantages of such studies, to anticipate some of our conclusions, accrues from the demonstration that on the whole good general growth or weight maintenance signifies a satisfactory ovulatory mechanism but not necessarily the ability to bear young — that ovulation in fact, when compared with implantation and placental function is a relatively hardy mechanism and that much if not most sterility must be traced to uterine failure. Such conclusions,

* Aided by grants from the American Red Cross and The Board of Research of the University of California. Generous donations of food materials have been made to ~~by~~ the University by the California Central Creameries.

however, can only come out of studies of the respective parts played by gonad and by uterus, so that it is apparent that studies on ovulation form a necessary part of a comprehension of the effect of diet on reproduction.

But we may emphasize also the fact that ovulation has nutritive relations which are not absolutely identical with those of the body as a whole — that absence of physical illness and the maintenance of body weight may yet be associated with gonadal failure — witness the war amenorrhea observed in the central countries during the recent war — and that conversely gonadal function may be stimulated or hastened by certain nutritive regimes as is amply demonstrated by the precocity of the mating season in sheep induced by the procedure of flushing.

There are other advantages in the study of each phase of the reproductive mechanism. The recognition of the time of oestrus enables the investigator to secure and record many instances of infertile congress and thus more easily and convincingly to acquire quantitative data on sterility. It is to be pointed out also that the usual method of securing data on reproduction is merely the record of litters born after pairing or mating animals for a few days. Such an attempt might involve merely the time of the dioestrous interval instead of oestrus and thus constitute no actual test, and it is more remotely possible that even if animals are mated for a longer time interval, individual male inactivity or habituation could interfere with the test. It would seem apparent consequently that the whole study of the relations between fertility and nutrition should employ these newer criteria for determining the exact time and steps in the reproductive function. During the last two years we have studied many nutritive regimes in this way, following American investigators whose work upon growth has become classic.

We wish to thank Professors E. V. McCollum, T. B. Osborne and L. B. Mendel, and H. C. Sherman for guidance and advice. We propose to discuss here the methods employed and certain general conclusions regarding the ovulation mechanism as influenced by quantitative and qualitative undernutrition. These conclusions will be supported by subsequent detailed papers on the separate aspects of the subject.

METHODS.

As a result of several years experience with the rat, we have maintained our colony in sterilizable metal cage units provided with water bottles and sliding tray bottoms, in which a few clean wood shavings are used for bedding and changed at frequent intervals. A cup similar to that employed by E. V. McCollum is attached to the back of the cage; the cup top makes it usually possible to feed finely granular food in a dry state, for it is difficult for the rat to pull food out over this rim. In the case of both young and adult animals, the full nutritional history is known and in many cases the nutrition of the parents. We have in all instances contrasted the behavior of animals with that of their litter mate sisters. Only in this way in our opinion may the investigator obtain the optimum conditions for a biological control in which genetic factors and the unknown factors in ~~slightly~~ varying food samples secured at different times or the seasonal behavior of animals may be all controlled together. Furthermore on account of wide individual variations in the behavior of rats we have used from six to twenty-four individuals for each test. The complete ovulation history of all animals is known by daily microscopic examination of the vaginal smear. The time of sexual maturity is thus determined with precision as the time of incidence of the first oestrus, and the lengths of successive oestrous cycles are compiled from the history as found on large individual record cards on which daily smear findings, weight, food intake and other data are entered.

The incidence of ovulation is indicated by the sudden occurrence and resolution of the typical oestrus vaginal smear which recurs every four or five days. The vaginal smear during the quiescent or dioestrous interval exhibits fair numbers of small irregular shaped nucleated epithelial cells, with which are always intermingled leucocytes. The onset of oestrus is heralded by characteristic changes in the vaginal smear, changes which thus mark off a distinct short premonitory epoch or pro-oestrus, during which leucocytes are no longer present and the less abundant irregular epithelial elements of the dioestrus are replaced by great numbers of strikingly uniform sized cells which solely characterize the smear and recur either singly or in sheets. Oestrus changes are inaugu-

rated by substitution of the small, nucleated and characteristic epithelial elements of the proestrus by large cornified non-nucleated squamous cells, which increase in numbers until they form a macroscopic cheesy detritus in the vaginal lumen in the last post-oestrus, which is about the time of ovulation. The occurrence of cornified cells may be designated for the sake of brevity as the occurrence of the oestrus vaginal smear. Leucocytes finally reappear as suddenly as they had previously disappeared and in very conspicuously increased numbers; the massive desquamation of the cornified elements ceases and they are succeeded by the sparse smaller nucleated irregular cells noted previously as present throughout the dioestrous pause. These epochs or steps in the oestrous cycle characterized by vaginal smears of (1) sparse epithelial cells and leucocytes, by (2) abundant nucleated epithelial cells only, by (3) cornified cells only, and by (4) cornified cells together with leucocytes, occupy time intervals of about 48, 12, 30 and 6 hours respectively, totaling 96 hours for the shortest normal cycle. Occasional cycles of 3 days are encountered and 5 day cycles may be considered normal, in fact are even more frequently encountered than 4 day cycles. The longer cycles are due normally to a prolongation of the dioestrous interval. Our individual record cards carry memoranda of the actual cells encountered in the daily smear. In our experience this is the only perfectly reliable oestrous or ovulation history, although cycles may be inferred from naked eye findings of the abundant cornified cell detritus of late oestrus and post oestrus.

ON THE INCIDENCE OF SEXUAL MATURITY AND THE LENGTH OF OESTROUS CYCLES IN ANIMALS ON A STANDARD NUTRITIONAL REGIME.

In 1920 Long and Evans reported statistical data upon the length of the oestrous cycle in some 300 healthy adults observed for periods varying from one to four months and maintained on generous diets of mixed table scraps. The length of some 2000 cycles was determined, 71% of which were of 4 and 5 days duration and 82% of 4 to 6 days. The general average was 5.4 days. Variation in the length of cycles was observed to occur not only in certain individuals which were more markedly irregular but as an occasional phenome-

non in histories of great regularity otherwise. For this reason a not inconsiderable number of longer cycles were encountered in such supposedly healthy animals on an abundant, varied, and supposedly adequate ration. They stated that, "Records of the succession of cycles in individual rats show such considerable variations that it may be said that only about 50% of all animals have cycles which may be depended upon to vary by less than two days in length. Even in the latter group, some individuals exhibit curious instances of a longer cycle interpolated in a long series of regular cycles of normal duration. One may also point out that a small proportion of all perfectly normal individuals exhibit such irregularity in their cycles as to be unavailable for experimental work". It became important to know to what extent these irregularities were due to unavoidable fluctuations in the food supply, the exact constitution of which in the form of table scraps was unfortunately unknown. We accordingly placed half of a large group (127) of young adults of from 85 to 148 days of age on a standard ration proven to yield good growth and reproduction by E. V. McCollum, permitting half of the group to continue on the table scrap ration and observing the ovulation rhythm for a period of about 50 days. The standard diet consisted of the following:

Wheat (whole ground).....	67.5
Casein	15.0
Whole milk powder.....	10.0
Sodium chloride	1.0
Calcium carbonate.....	1.5
Butter fat	5.

The animals, to judge from body weight and other signs of health, tolerated well this sudden change in the physical consistency of their diet. The standard nutritional regime did not significantly change the oestrous rhythm, as the subjoined table will show.

TABLE 1.

Ovulation performance of group of young adults rats, approximately half of which were maintained on a table scrap diet, half on a standard diet. (The animals had all been reared on a table scrap diet).

STANDARD DIET.

(number of animals 76)

Length of oestrous cycle.	Number of instances		Percent of all cycles.
3 day cycles.....	13	13	1.7 %
4 " "	291	580	74.6 %
5 " "	289		
6 " "	92	184	23.7 %
7 " " and over...	92		
	777		100.0 %

Average length of cycle — 5.3 days.

TABLE SCRAP DIET.

(number of animals 51)

Length of oestrous cycle.	Number of instances		Percent of all cycles.
3 day cycles.....	4	4	.9 %
4 " "	167	341	81.1 %
5 " "	174		
6 " "	55	76	18.0 %
7 " " and over...	21		
	421		100.0 %

Average length of cycle — 5.07 days.

When experiments were done with litter mate sisters as the controls and the observations extended to about 150 days, the results were still not substantially different from the above, as the subjoined table will show.

TABLE 2.

Ovulation performance of group of young adult rats on a standard diet, litter mate controls on table scrap diet. (The animals had all been reared on a table scrap diet).

STANDARD DIET.
(number of animals 21)

Length of oestrous cycle.	Number of instances		Percent of all cycles.
3 day cycles.....	4	4	.7 %
4 " "	214 }	423	80.5 %
5 " "	209 }		
6 " "	62 }	98	18.6 %
7 " " and over...	36 }		
	525		99.8 %

Average length of cycle — 5.01 days.

TABLE SCRAP DIET.
(number of animals 21)

Length of oestrous cycle.	Number of instances		Percent of all cycles.
3 day cycles.....	1	1	.2 %
4 " "	163 }	378	76.2 %
5 " "	215 }		
6 " "	74 }	117	23.6 %
7 " " and over...	43 }		
	496		100.0 %

Average length of cycle — 5.21 days.

In both series of experiments, from seventy-four to eighty per cent. of the oestrous cycles observed in animals on either of the nutritive regimes were of the normal four or five days duration.

These animals were all selected individuals in good health, and the dietary regularity which we imposed did not further decrease the low number of irregular cycles. It appeared consequently that an irregularity of this degree could not be ascribed to variations in nutrition.

The adequacy of the standard diet seemed assured, inasmuch as such phenomena as weight maintenance and the ovulation rhythm were essentially the same in animals fed the standard regime as in those fed bountifully on table scraps. Such a conclusion, however, seemed to us most rigorously tested by the performance of animals actually reared from

the time of weaning (21st day) on these two regimes. We accordingly picked a group of thirty healthy suckling animals and on the twenty-first day of life divided them into two lots, rearing one lot on the standard nutritional regime and the other on generous miscellaneous table scraps secured from adjacent large hotels. From each litter so far as possible an equal number of animals were placed on either of the two diets. The groups were observed for almost five months.

TABLE 3.

Ovulation performance of group of rats reared on the standard diet, litter mate controls, reared on a table scrap diet.

STANDARD DIET.

(number of animals 14)

Length of oestrous cycle.	Number of instances		Percent of all cycles.
3 day cycles.....	2	2	.7 %
4 " "	107	224	85.5 %
5 " "	117		
6 " "	25	36	13.7 %
7 " " and over...	11		
	262		99.9 %

Average length of cycle — 4.9 days.

TABLE SCRAP DIET.

(number of animals 16)

Length of oestrous cycle.	Number of instances		Percent of all cycles.
3 day cycles.....	12	12	4.1 %
4 " "	129	241	83.7 %
5 " "	112		
6 " "	22	35	12.1 %
7 " " and over...	13		
	288		99.9 %

Average length of cycle — 4.7 days.

It will be seen that the animals on the standard diet matured as early and exhibited as large a proportion of short (four

and five day) oestrous cycles as did their sisters on table scrap rations. Nor did the growth exhibited by the two groups vary significantly. Figure 1 shows the average of growth of each group, together with the extremes observed. It will be noted that in the later phases, the growth on table scraps tends slightly to exceed that observed in animals on the standard nutritional regime.* The ovulation history of the two groups was nevertheless practically identical.

PERFORMANCE OF A LARGE GROUP OF ANIMALS ON THE STANDARD NUTRITIONAL REGIME.

Inasmuch as many animals reared on the standard diet had to be used as controls for animals on defective diets, we have reared somewhat over 500 individuals from the twenty-first day of life (time of weaning) on this regime. Since Long and Evans have shown that the first four oestrous cycles are considerably longer than those following**, these have been omitted from our computations. Our results did not differ materially from those obtained from adults which had been reared on table scraps. All groups taken together permit us to present data for a very large number (10,000) of cycles of animals while on the standard nutritional regime:

* We are investigating this further by the study of animals for a period of a year or more.

** Although cycles of 4 and 5 days in length comprise over 70% of all subsequent cycles, in the case of the first four cycles, data secured from about 400 animals have yielded the following — only 23% of first cycles are of this length (4 and 5 days), 38% of second cycles, 41% of third and 54% of the fourth cycles. While the average length of all cycles is 5.4 days, that of first cycles is 8.0 and that of fourth cycles 6.0 days.

TABLE 4.

Table showing length in days of oestrus in animals on a standard nutritional regime (10,000 cycles).

Cycle length in days	Number of observed instances	Percent of all cycles.
3	72	52 0.72
4	3494	34.94
5	3943	39.43
6	1439	14.39
7	380	} 24.91 %
8	213	
9	96	
10	128	
11	39	
12	36	
13	47	
14	33	
15	25	
16	12	
17	9	} 10.52
18	13	
19	9	
20	3	
21	4	
26	1	
28	2	
31	1	
49	1	

General average, 5.4 days.

In the case of such a large group of animals reared from the time of weaning on a standard diet, it was possible for us for the first time to inquire into variations in the time of advent of sexual maturity. At or before this time occurs the rupture of the solid epithelial core which closes the vaginal canal and which has become a glistening membrane over the site of the future orifice. This may either be coincident with or occur a day or two before the first oestrous changes in the vaginal mucosa. In rarer cases the latter event is postponed for a week or more. In cases of undernutrition, the final breakdown of the vaginal closing membrane may be totally dissociated from the incidence of the first oestrus. The sub-joined tables present in detail these data on sexual maturity. It will be noted that the approximate age of 60 to 70 days for maturity as given by Donaldson (*The rat*, Philadelphia, 1915) differs somewhat from what may be attained by animals on a superior nutrition, in which a relative precocity results.

Graphs of the best, of the poorest and of the most frequently occurring growth are presented in figure 2.

TABLE 5.

Table showing ages at sexual maturity of 570 rats.

Day of life	Number of individuals in which the rupture of the membrane closing the va- ginal orifice occurred on this day.	Number of individuals in which first oestrus occurred on this day.
30	1	
31		
32	2	1
33	1	2
34	5	4
35	7	6
36	8	5
37	15	12
38	12	9
39	26	16
40	24	14
41	26	21
42	35	30
43	39	36
44	36	26
45	37	35
46	35	31
47	35	34
48	38	32
49	25	25
50	22	21
51	34	32
52	21	25
53	16	20
54	14	20
55	21	20
56	8	9
57	2	4
58	6	10
59	5	12
60	7	4
61	5	5
62	4	7
63	3	5
64	2	6
65	2	7
66	1	4
67	0	3
68	0	2
69	0	0
70	0	4
71	1	3
72	1	0
73	0	2
74	0	1
75	0	1
76	1	0
77	1	1
81	0	1
82	0	1
94	0	1

TABLE 6.

Tabular Summary of Occurrence of First Oestrus in 570 Individuals.

Age in days	Number of instances of 1st oestrus	Per cent
32-36	18	3.1
37-55	459	80.5
(42-48)	(224)	(39.2)
56-66	73	12.8
67-77	20	3.5

Average age at opening of vagina 46.8 days

Average age at first oestrus 47.3 days

SUMMARY.

The present communication aims to lay a foundation for the study of aberration in ovulation due to defective diet. It attempts to establish the time of occurrence of the first oestrus and the normal ovulatory rhythm in rats maintained on a satisfactory nutritional regime. A large group of animals have been tested. The determination of the rate of growth shows that we are dealing with individuals whose performance in that respect is equal to, or in fact clearly better than that hitherto recognized as the norm for this species. Comparisons have been made between the performance of animals on a generous and varied diet in the form of abundant table scrap rations, and animals on a standard nutritional regime. Significant differences in the behavior of the two groups were not observed. It is possible to state that in eighty per cent. of animals handled in this way the first oestrus occurs between the thirty-seventh and the fifty-fifth day of life, on the average on the forty-seventh day, and that when a sufficient number of oestrus cycles are observed about three-fourths of all oestrus cycles are five days or less in length, approximately one fourth being of longer duration.

EXPLANATION OF FIGURES.

Figure 1. Graph of growth exhibited by thirty female rats, half of which were reared on the standard diet, half (litter mate sisters)

on a table scrap ration. The three double curves represent the average (middle) and the extremes (upper and lower) of growth. The upper curve in each of the three groups represents the growth on the table scrap ration.

Figure 2. Showing in heavy line the mode of growth of 535 females reared on the standard diet. The small circle on the line denotes the average time of occurrence of the first oestrus. Extremes of growth are shown by lighter lines.

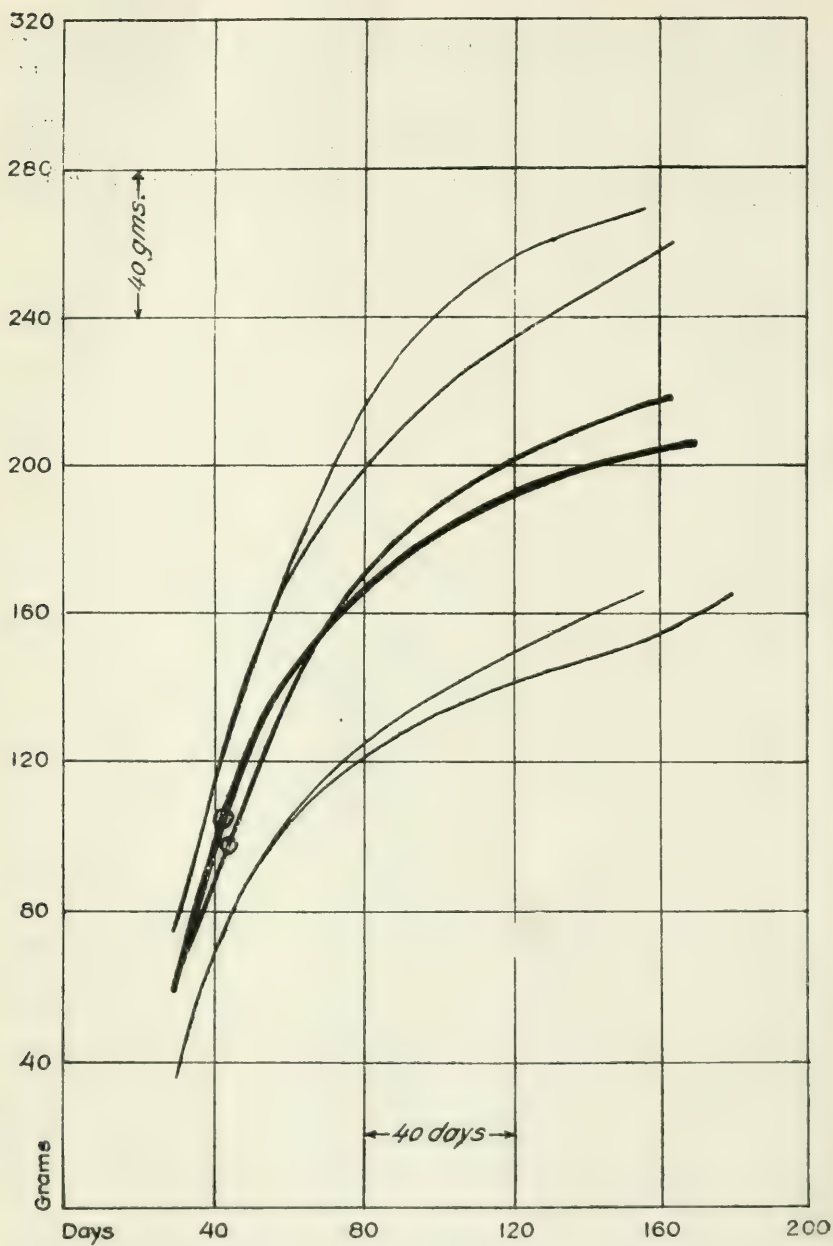


FIGURE 1.

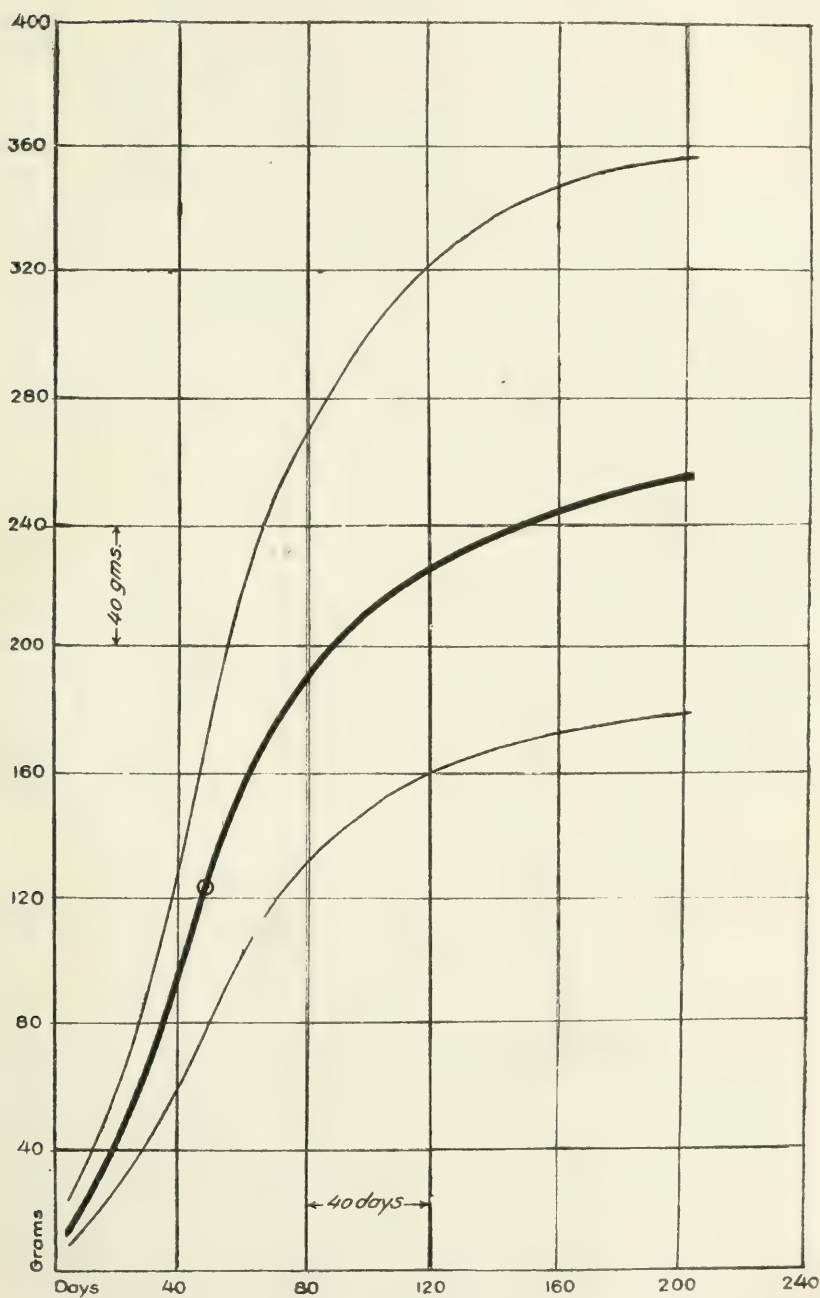


FIGURE 2.

ON THE RELATIONS BETWEEN FERTILITY AND NUTRITION *

II. — THE OVULATION RHYTHM IN THE RAT ON INADEQUATE NUTRITIONAL REGIMES.

BY HERBERT M. EVANS AND KATHARINE SCOTT BISHOP

From the Anatomical Laboratory of the University of California

We propose to summarize here the general results of experiments involving several hundred individuals, conducted during the last two years. A short series of subsequent papers will present the detailed data upon which the conclusions rest.

1. — THE EFFECT OF UNDERNUTRITION WITH A BALANCED DIET.

(a) *Attainment of sexual maturity.* It has been previously shown that a diet consisting of whole wheat, whole milk powder, casein and salts (a diet suggested by E. V. McCollum and designated by us Standard Diet I) constitutes an adequate nutritional regime both for growth and for reproductive performance in the rat.

Standard Diet I.

whole wheat.....	67.5
casein	15
whole milk powder...	10
sodium chloride	1
calcium carbonate	1.5
butter fat	5

We have limited the consumption of this diet (which must be still regarded as adequate or "balanced" in its proportions) so as to create conditions of partial starvation and stunting. Three different nutritional levels were maintained, resulting in three corresponding weight levels, namely 200 grams, 125-150 grams and 60-85 grams approximately (see figure 1). This

* Aided by grants from the American Red Cross and The Board of Research of the University of California. Generous donations of food materials have been made the University by the California Central Creameries.

was accomplished by determining the daily food consumption of the controls (littermate sisters in all cases) and reducing it slightly for the first group (200 gram rats), reducing to about two-thirds for the second group (125-150 gram rats), and practically halving it for the third group (60-85 gram rats). The food dosage permitted occasional slight growth, particularly in the 200 gram group, which were not actually maintained at a level but grew continually, though at a slower rate than the normal controls. The rats so treated and their controls were observed, with daily microscopic examinations of the vaginal smear to determine the occurrence of oestrus and ovulation, for a period of 375 days.

The most seriously stunted group consisted of animals not one of which for the period of 375 days ever exhibited an oestrus cycle, although rupture of the vaginal closing membrane occurred at some time between the 87th and 117th day of life (on the average at the 99th day).

In the case of animals maintained at a weight level of 125 to 150 grams, eight of the ten animals observed for 375 days eventually exhibited oestrus. The first oestrus in this group was detected at times varying from the 116th to the 332nd day of life, the average age being at about the conclusion of the seventh month, but two of such individuals which were maintained for over a year at weight levels varying from 130 to 150 grams failed entirely to exhibit ovulation.

The first group (200 gram rats), in which the nutrition was not so seriously affected, demonstrated nevertheless that we had affected seriously the ovulatory performance. There was corresponding delay in the appearance of the first oestrus, which though varying from the 50th to the 135th day occurred on the average at the 67th day of life, in contrast to maturity before the 50th day of life which occurred in normal controls.

It is evident from the above that general or quantitative undernutrition, depending upon its degree, may either entirely prevent or postpone the attainment of sexual maturity. It is evident that in the more seriously affected group of individuals we have succeeded in eliminating the influence of gonadal function, whatever that may be, and that we have thereby an opportunity to investigate processes of growth or differentiation which are supposedly dependent upon or related to that function.

(b) *Ovulation rhythm.* The ovulation rhythm of the individuals belonging to the second of the above groups—animals maintained at a weight level of approximately 140 grams—is gravely affected, as would be inferred from the facts presented regarding the appearance of the first oestrus. In a 375 day period, ten rats behaved as follows: two had no oestrus, one had no ovulation cycle except for the first oestrus, while out of the remaining seven one had 1 cycle, four had 2 cycles, and two had 3 and 4 cycles respectively.

We have already inferred that in the first or most normal group ovulation was affected, although growth of some single individuals is within normal limits. Twelve 200 gram rats, studied for seven months only, show a maximum of 14 cycles in any one case (varying from 1 to 14, averaging 7 each), while their littermate controls during this period have from 10 to 38 cycles each, or average 25 cycles apiece. Only two of the 200 gram rats were observed for an entire year, showing 25 cycles as the maximum number of ovulations in any one individual in that time, while its control had 55 cycles. The times of oestrus in the experimental group were thus almost invariably separated by long intervals. Should we continue to designate the time from the exhibition of one oestrus to the next as a cycle, but 14% of all such "cycles" shown by the 200 gram rats are of the normal length of five days (controls, 76%) and most of them are of very great length. It is rather remarkable to see this abnormality in animals not greatly underweight—not more so, for instance, than the lighter members of a large normal group on an adequate nutrition. In the latter case animals which may be designated natural "runts" exhibit a time of maturity and an oestrus rhythm completely normal in nature. It is to be noted that the indices of ovarian function overlap in these two groups as well as the growth rates, although in general the ovulation histories are strikingly different (i.e., one control has but 4 cycles in seven months, of which 8 are very long, although its growth rate is within the normal; a second control has but 12 cycles in this period and is one of the most rapidly growing rats).

To summarize, underfeeding affects the time of maturity and ovulation history. The amount of delay in maturing and

the degree of suppression of oestrus changes vary according to the degree of starvation to which the animal is subjected, and although not correlated exactly with body weight changes or variation in growth rate, in general the greater stunting results in the more marked disturbance of the ovulation rhythm.

2. — EFFECT OF CHANGES IN THE PROPORTIONS OF CARBOHYDRATE, FAT AND PROTEIN.

The supposed value of the maintenance of certain proportions among the three fundamental food categories (fats, carbohydrates and proteins) would appear not to have been submitted to rigorous experimental test. We know the indispensability of a definite protein intake for nitrogen balance and of a further amount for growth. Solution of the problem of whether fats and carbohydrates may both be deemed essential or beneficial would appear to have been advanced recently by the discovery of Osborne and Mendel that the rat will grow well on a dietary almost, if not entirely, lacking in fat or in preformed carbohydrate. We have shown that maintenance of the ovulation rhythm and capacity to bear young constitute a more exacting test of a sound physiology than does growth alone. It would, accordingly, seem important to apply such a test to animals reared under such conditions. It was possible for us to investigate not only the approximate absence of formed carbohydrates or of fat from a dietary but also the effect of high or low proportions of protein. We have employed fat free (really only fat low) diets consisting of cornstarch, casein and salts, varying the proportion of casein so that this constituted respectively 12, 23, 50 and 91 per cent. of the diet. A similar thing was done with mixtures of lard, casein and salts so that preformed carbohydrates were absent. In both groups the vitamine requirements were satisfied by feeding separately daily 0.4 gram of dried whole yeast in a thin syrup of sugar and water and either 0.2 gram of dried alfalfa leaves or, in the group of diets containing lard, by a 5% butterfat content. In each case twelve animals were chosen for experimentation and twelve littermate sisters were maintained on a standard diet consisting of casein, cornstarch, lard and butter (Standard Diet II.).

Standard Diet II.

casein	18
cornstarch	54
butter fat.....	9
lard	15
salts	4
0.4 gram dried yeast daily	

Carbohydrate-free Protein 12

casein	12
lard	60
butterfat	18
agar	5
0.4 gram dried yeast daily	

Carbohydrate-free Protein 23

casein	23
lard	58
butterfat	9
salts	5
0.4 gram dried yeast daily	

Carbohydrate-free Protein 50

casein	50
lard	36
butterfat	9
salts	5
0.4 gram dried yeast daily	

Carbohydrate-free Protein 91

casein	91
butterfat	5
salts	4
0.4 gram dried yeast daily	

Fat-free Protein 12

casein	12
cornstarch	83
salts	5
0.2 gram dried alfalfa daily	
0.4 gram dried yeast daily	

Fat-free Protein 23

casein	23
cornstarch	72
salts	5
0.2 gram dried alfalfa daily	
0.4 gram dried yeast daily	

Fat-free Protein 50

casein	50
cornstarch	45
salts	5
0.2 gram dried alfalfa daily	
0.4 gram dried yeast daily	

Fat-free Protein 91

casein	91
cornstarch	4
salts	5
0.2 gram dried alfalfa daily	
0.4 gram dried yeast daily	

The period of observation for some animals in every group has extended over 240 days and in no case for less than four months. Growth was recorded by weighings every five days (see figures 2 and 3).

As the condensed table will show, animals on carbohydrate free diets in which protein was neither very high nor low, grew at an approximately normal rate; nor was there in either case significant injury to the sex physiology due to carbo-

hydrate absence. When compared with the controls, the time of maturity was not delayed and the proportion of short oestrus cycles was not significantly decreased.* On the other hand, with very low protein (12 per cent.) the carbohydrate free diet consisted so largely of lard and butter as to interfere greatly with palatability, and the animals refused to consume enough protein for growth requirements (average daily intake 6.7 grams against 10.8 grams of controls); a great stunting resulted and, as is invariable in our experience with nutritive stunting, a delay in the attainment of maturity (average 121 instead of 69 days) and fewer oestrous periods. The carbohydrate free diet with 91 per cent. of casein produced a somewhat deleterious effect on growth and hence on the sexual physiology, but these effects would appear to be due solely to the disadvantage under which the animals suffered from the high protein and not to the withdrawal of carbohydrate, for as regards growth the same depression occurred in animals maintained on the fat free, high protein (91 per cent.) mixture. Nutritive regimes involving the withdrawal of carbohydrate would hence not seem to be in themselves deleterious to the rat.

Much interest attaches to the physiological effects of the withdrawal of fat. Our study of the incidence of maturity and sequence of oestrous cycles shows an evident deleterious effect of the fat free diets and an effect in excess of that portrayed by growth inadequacy. Nevertheless the ill effect of fat deficiency is least (being almost masked) when protein constitutes 23 or 50 per cent. of the diet. When protein is low (12 per cent.) it is remarkable that growth on a fat free diet may be practically normal and yet a depression of the function of the sex glands is very evident. Maturity is postponed and ovulation is far less frequent. With high protein, fat inadequacy shows up with similar emphasis and the delay in maturity and poor oestrous rhythm are more evident than in any of the fat free groups. Nor can we allow this effect to be due predominantly to the high protein alone, for it is in great excess of the effect of carbohydrate free, high protein rations. Future discovery may show similar functional deficiencies of other organs when animals are reared and held

* The reader will note the poor performance of the littermate sister controls on the Standard Diet II. when compared with animals on a superior dietary as recorded in our first paper. This will be specifically commented upon at the close of the paper.

on fat free diets. For the present we may state that in such circumstances, a completely normal growth is nevertheless associated with outspoken injury to the organs of sex.

SUMMARY OF THE EFFECTS OF FAT AND CARBOHYDRATE FREE DIETS.

(Littermate controls reared on Standard Diet II.)

Diet	Age in days at first oestrus	Total number of cycles observed	Percent of 4 and 5 day cycles*	Growth as compared with controls
COH free Protein 12	121 (48-371)	43	23	40-90 grams lower than controls from 50th day on.
Standard II.....	69 (39-144)	147	57	
COH free Protein 23	74 (47-108)	111	48	Slightly (10 grams) below controls, occasionally identical or above.
Standard II.....	74 (39-144)	151	51	
COH free Protein 50	65 (40-97)	190	56	Identical or slightly above until 125th day when they fell below. 30 grams below at 225th day.
Standard II.....	77 (39-112)	198	99	
COH free Protein 91	118 (61-188)	53	47	25-60 grams lower than controls from 50th day on.
Standard II.....	73 (45-144)	189	68	
Fat free Protein 12.	88 (48-150)	69	35	10-20 grams below controls until after 200th day when identical.
Standard II.....	66 (39-119)	153	56	
Fat free Protein 23.	65 (42-80)	100	46	Identical until 75th day, then 10-15 grams below controls.
Standard II.....	66 (39-96)	115	52	
Fat free Protein 50.	92 (46-156)	33	45	Identical until 75th day, then 20-25 grams below controls.
Standard II.....	62 (39-96)	95	42	
Fat free Protein 91.	160 (71-253)	0	1	30-70 grams lower than controls from 50th day on.
Standard II.....	58 (39-83)	106	45	

3. — UNDERNUTRITION DUE TO QUALIFICATIVE DEFICIENCY OF THE PROTEIN.

We have repeated the classical experiments of McCollum, Osborne and Mendel, and others which show the inadequacy

* Outspoken injury cannot be assumed except when this figure falls below 40 since some controls are at 42, although the figure 42 is very low for standard. The reader will remember that 75 per cent. of cycles are of 4 and 5 day length on the best nutritional regime.

of the protein of wheat when this grain is used as the sole source of protein. A dietary after McCollum was followed:

Diet 5.

wheat	60
sodium chloride	1
calcium carbonate.....	1.5
dextrin	32.5
butter fat	5

Although adults are apparently not injured by being placed for relatively long periods (100 to 200 days) on this diet, young animals are badly stunted if reared upon it. Such animals average but 95 grams on the 100th day and do not grow appreciably beyond this (102 grams on the 275th day). Nor do such animals behave differently in their sexual physiology from "runts" created by quantitative undernutrition. Of a group of thirteen, seven had no oestrous periods during the 165 days of observation, while the remainder have shown the first ovulation or maturity at the 47th, 54th, 70th, 76th, 123rd and 140th day. Only three of these six individuals have exhibited other ovulations; one has had 2 cycles in 76 days, one 7 in 118 days, and one 8 in 114 days. During the same period of time their littermate sisters have matured and experienced, on the average, 20 cycles. There is nothing to indicate that the injury to sexual physiology would be lessened or disappear as long as the nutritive regime was maintained (one rat maintained on it and observed for 275 days had no oestrous). On the other hand, we have effected restoration by the addition of casein to the diet.

4. — EFFECT OF DEFICIENCY IN SALTS.

Although marked defect in ability to grow cannot be said to show itself as a result of diets poor in the salts (see figure 4), yet such diets give a definite effect on oestrous phenomena. When the salts of our Standard Diet I. (casein - whole wheat - whole milk diet) are omitted and the only salt present is that found in the above three ingredients, maturity is somewhat delayed (occurring on the average on the 67th instead of the 56th day) and only 70 per cent. of the cycles are short ones as against 77 per cent. shown by littermate controls on Standard Diet I. with salts.

Standard Diet I. without salts.

wheat	70
casein	15
whole milk powder.....	10
butter fat.....	5

When salts are omitted from Standard Diet II. (casein - butter - lard - cornstarch ration) the oestrous rhythm is, as might be expected, more gravely affected, only 15 per cent. of the cycles being of the 4 or 5 day length as against 48 per cent. of those of littermate controls, while the experimental rats mature at an average age of 66 days against an average maturity at 60 days shown by their controls on Standard Diet II. (formula given above).

Standard Diet II. without salts.

casein	19
cornstarch	56
lard	15.75
butter fat	9.25
distilled water used.	
0.4 gram dried yeast daily.	

It is evident that the sex impairment is much in excess of the impairment of growth; that in a way unknown to us salt depletion is inimical not only, for instance, to skeletal growth, but to the normal rhythm of ovulation.

5. — DISTURBANCE DUE TO REDUCTION IN THE SUPPLY OF FAT SOLUBLE VITAMINE A.

As may be inferred from their tolerance in other respects, adult rats which have previously lived on an adequate diet may be placed for long periods on diets low in vitamine A and show no detectable ill effects. Thus adults reared on Standard Diet I. (whole wheat - casein - whole milk ration) containing 5% of butter fat besides that in the milk, which has constituted our standard, may be shifted to the same ration from which the 5% butter has been withdrawn and for at least 100 days regular ovulation rhythm will be maintained, about 20 cycles resulting.

Standard Diet I. without butter.

wheat	67.5
casein	15
skim milk powder.....	10
sodium chloride	1
calcium carbonate	1.5
lard	5

The diet which we have designated Diet 2 in our list and which McCollum has shown to be deficient in its vitamine A content may be fed healthy adults for as long as 200 days without physiological ill effects detectable in oestrous. There is weight maintenance or, in some cases, even increase in weight on this diet.

Diet 2.

rolled oats.....	40
gelatin	10
casein	5
salt mixture (185)	3.7
dextrin	40.3
butter fat	1

When, however, adult animals with an excellent nutritive history are placed upon a diet more seriously deficient in vitamine A, their period of immunity from disturbance is not so great. When placed upon a mixture of casein, cornstarch and lard with a daily dried yeast ration (0.4 gram) to satisfy the vitamine B requirement, such adults usually show disturbance of their ovulatory rhythm somewhat before the 100th day, but at times varying in a group of thirteen animals from the 73rd to the 130th day.

Standard Diet II. without butter.

casein	18
cornstarch	54
salts	4
lard	24
0.4 gram dried yeast daily.	

The disturbance of oestrous from fat soluble vitamine A deficiency is highly characteristic, resembling no other nutritive upset known to us. It consists in the prolongation of the oestrous desquamative change in the vaginal epithelium, the

smear consisting chiefly, if not exclusively, of the cornified cells which in normal individuals characterize the actual period of oestrous and ovulation only, but which, in the case of animals showing vitamine A deficiency, occur throughout the entire period of acute deficiency. Usually when the test is given, other signs of vitamine A deficiency such as weight decline have appeared but this characteristic continuance of the oestrous smear may precede all other signs of lack of vitamine A and, furthermore, is shown in conditions where vitamine A is not so low as to cause growth failure or xerophthalmia. It may thus constitute the only sign of vitamine lack save failure to reproduce successfully. Since the continuance of oestrous changes in the ovary and vaginal epithelium represents in both localities cell activity and growth, we are to understand that the lack of this nutritive element provokes an abnormal physiology or dysfunction of the reproduction system. In this respect the ill effects of vitamine A deprivation are entirely different from those resulting from the withdrawal of vitamine B., which has as its sequel complete cessation of ovarian function. Animals submitted to the degree of vitamine A deficiency giving the above test, however, continue to ovulate and to form corpora lutea irregularly or at intervals approximating the normal.

Evidence that the body stores and utilizes stored vitamine A is adduced by many types of experiments, but is convincingly shown by our new test for vitamine A deficiency. When adults instead of having an excellent nutritive past history have had to exist for 80 days on a casein - cornstarch - lard ration with only 2% butter fat and when they now have all butter fat withdrawn, they develop the sign of vitamine A deficiency on the average in 68 instead of the 100 days required when the diet before butter withdrawal was identical but contained 9% butter fat. When animals have had a still poorer nutritive past and have been reared from the time of weaning on the casein - cornstarch - lard - 2% butter regime, the withdrawal of butter may give our vitamine A deficiency sign within 4 days, always does so by the 44th day and usually within 14 days.

Animals may be reared on a ration low in vitamine A but high enough to prevent the exhibition of our sign throughout their life (Diet 2, formula given above). Their offspring, how-

ever, reared on the same diet may show this sign spontaneously or at about the 100th day of life, evidence that the stores of vitamine A derived from the mother and early life were finally inadequate (see figure 5).

Animals may be reared on a ration low in vitamine A but high enough to withhold the exhibition of our sign until the 100th day of life — 78th to 120th day — (Standard Diet I. without butter, formula given above). Under such circumstances they show an almost normal rate of growth, reaching 250 grams on the 300th day of life (figure 5) and they mature at about the normal time. There is complete absence of eye disease. Their deficiency could not be suspected save by failure to breed, but it is plainly evidenced before their final decline and usually for many weeks or even months before this event by the new sign.

When rats are reared from the time of weaning (21st day) on a diet less adequate in vitamine A — for instance, on the cornstarch - casein - lard ration without butter (Standard Diet II. without butter), in addition to showing the same poor oestrous rhythm, they exhibit the characteristic aberration of oestrous here described at about the 90th day of life, at a time when in most cases growth decline has not yet or has barely started to manifest itself (see figure 6). Indeed, if the casein in the last mentioned ration is extracted with alcohol to reduce still further the content of fat soluble vitamine A, the characteristic oestrus abnormality may appear so early as to be coincident with or within ten days of the date of maturity (52nd to 60th day of life), and in every case in our group of twelve rats the change from normal is completed by the 100th day of life.

6. — DISTURBANCE DUE TO REDUCTION IN THE SUPPLY OF WATER SOLUBLE VITAMINE B.

When in the diet consisting of cornstarch, lard and casein the daily supporting dose of 0.1 gram of dried yeast is withdrawn, animals fail in weight rapidly, as is well known, but in practically all cases cessation of oestrus occurs at once and if the yeast dosage is merely decreased, oestrus cycles may fail to occur and yet weight be maintained. On the other hand, animals reduced in weight and without cycles as a result of withdrawal of vitamine B will gain weight immediately when

even a slight amount of yeast is fed, but will not have cycles for some time. Thus ovulation responds more sensitively to this lack than does general bodily nutrition. Oestrus is not prolonged in the characteristic way as with vitamine A deficiency, but is obliterated, the ovarian follicular apparatus coming to a condition of complete rest. When an attempt is made to rear rats on the above ration without yeast, growth, as is well known, fails and even if life is maintained by means of an occasional yeast dose, severe stunting results. Such animals may never exhibit an oestrous cycle or mature only after great delay. Every stimulus to growth given by an administration of yeast may be accompanied by a short period during which ovulations succeed one another at a normal or almost normal rate.

7. — DISTURBANCE OF OVULATION RHYTHM ON DIETS CONSISTING OF SINGLE, NATURAL FOODSTUFFS.

We cannot confirm the prevalent opinion that rats will fail entirely on a purely carnivorous diet (see figure 7). Twelve animals were fed freshly boiled beef cheek muscle with an abundance of water. Such animals grow at a not markedly subnormal rate (225 grams on the 150th day of life as against 240 grams of the controls), but their maturity does not occur on the average until the 100th day and but 43 per cent. of oestrous cycles are of the normal short duration.

Animals forced to subsist on milk, either fresh or as whole dried powder, give outspoken evidence of an abnormal physiology of sex, and yet, here also, growth is not significantly depressed (190 grams on the 175th day of life). Five animals have been fed on a ration of fresh milk alone for a period now of 175 days (see figure 7). The performance of perfectly normal controls in this time would have led to a total of about 20 oestrous cycles apiece. During this time one of the animals has not experienced a single oestrus and the remaining four have matured on the average at the 110th day. Two have shown no ovulations since the first oestrus and the remaining two have shown but 4 and 9 ovulations respectively. The record for the same time of six animals, littermate sisters to these, but maintained on a diet of dried whole milk (Merrill-Soule) is not materially different. Here also one animal has not matured at the 175th day and the remainder, although matur-

ing at the 80th day on an average have ovulated respectively but 1, 1, 2, 6, and 6 times.

8. — DISTURBANCE OF OVULATION RHYTHM ON SUPPOSEDLY ADEQUATE DIETS.

In observing the ovulation performance of animals fed on the casein-lard-cornstarch ration supplemented by salts, yeast and butter, the ration which we have called Standard Diet II. (formula given above) the reader will already have become aware of inferior function in such animals when compared with those under the best conditions known to us and tabulated in our first paper. The ratio of 4 and 5 day oestrous cycles may fall to 42%. We would emphasize that these animals exhibit what would be designated a normal rate of growth (at least 220 grams on the 200th day). It is evident that their physiological state cannot properly be said to equal that of animals maintained on the diets mentioned in our earlier work. To what is the difference due? We hope in future work to be able to elucidate this problem and shall content ourselves here with pointing out that a dietary regime which has been employed in some classic investigations on nutrition and has won general acceptance as a standard from which subtractions, for instance, would enable us to measure vitamine adequacy (see Eddy, 1921) is itself inadequate to confer a sound physiological condition upon the animal body. Nor would it appear beyond the necessary deductions from our work for us to regard the results of the study of ovulation as compelling us to recognize more sensitive tests of wellbeing than that furnished by the growth rate. Animals that grow normally or at least within the limits to be recognized as those of the normal rate, may be so seriously impaired in their organs of reproduction as to depart widely from the normal ovulation rate. We are, furthermore, able to demonstrate that fecundity and fertility are reduced before upset to the ovulation rate and that when the latter occurs the impairment is a grave one.

FIGURE 1. — *Quantitative undernutrition.* The three heavy lines are average growth rates of three groups of underfed rats. Average growth rate of littermate controls reared on an abundance of Standard Diet I is shown in the lighter line. Circles mark average times of occurrence of first oestrus.

FIGURE 2. — *Carbohydrate free diets.* Heavy lines show average growth rates of rats reared on carbohydrate free diets containing 12, 23, 50 and 91 per cent. of protein respectively, as labelled. Average growth rates of littermate controls reared on Standard Diet II are shown in lighter lines. Circles mark average time of appearance of first oestrus.

FIGURE 3. — *Fat free diets.* Heavy lines show average growth rates of rats reared on fat free diets containing 12, 23, 50 and 91 per cent. of protein respectively. Average growth rates of littermate controls reared on Standard Diet II are shown in lighter lines. Circles mark average times of occurrence of first oestrus.

FIGURE 4. — *Salt low diets.* Heavy lines show average growth rates of rats reared on diets low in salts, as labelled. Average growth rates of littermate controls reared on Standard Diets I and II respectively are shown in lighter lines. Average times of occurrence of first oestrus are marked by circles.

FIGURE 5. — *Diets low in vitamine A.* The two upper curves show average growth rates of rats reared on Standard Diet I with (lighter line) and without (heavy line) butter fat. The three lower curves show average growth rates of rats reared on Diet 2 which contains 1% butter fat (heavy lines, first and second generations as labelled) and littermate controls of the first generation, reared on Standard Diet I (lighter line). The circles mark average times of occurrence of first oestrus and the pairs of parallel lines mark average times of appearance of the abnormal ovulation cycles characteristic of lack of vitamine A.

FIGURE 6. — *Diets low in vitamine A.* Heavy lines show average growth rates of rats reared on Standard Diet II without butter fat, Standard Diet II with 2% butter fat and Standard Diet II without butter fat, casein extracted with alcohol, as labelled. Lighter lines show average growth rates of littermate controls reared on Standard Diet II. Circles mark average times of occurrence of first oestrus. Pairs of parallel lines mark average times of appearance of abnormal cycles characteristic of lack of vitamine A. At the point shown by the single line on the curve for rats reared on 2% butter fat, all butter fat was withdrawn from the diet.

FIGURE 7. — *Meal and milk diets.* Heavy lines show average growth rates of rats reared on beef muscle alone, fresh milk and whole milk powder alone, as labelled. Controls (littermates of the beef muscle group), shown in lighter line, were reared on Standard Diet I. Circles mark average times of occurrence of first oestrus.

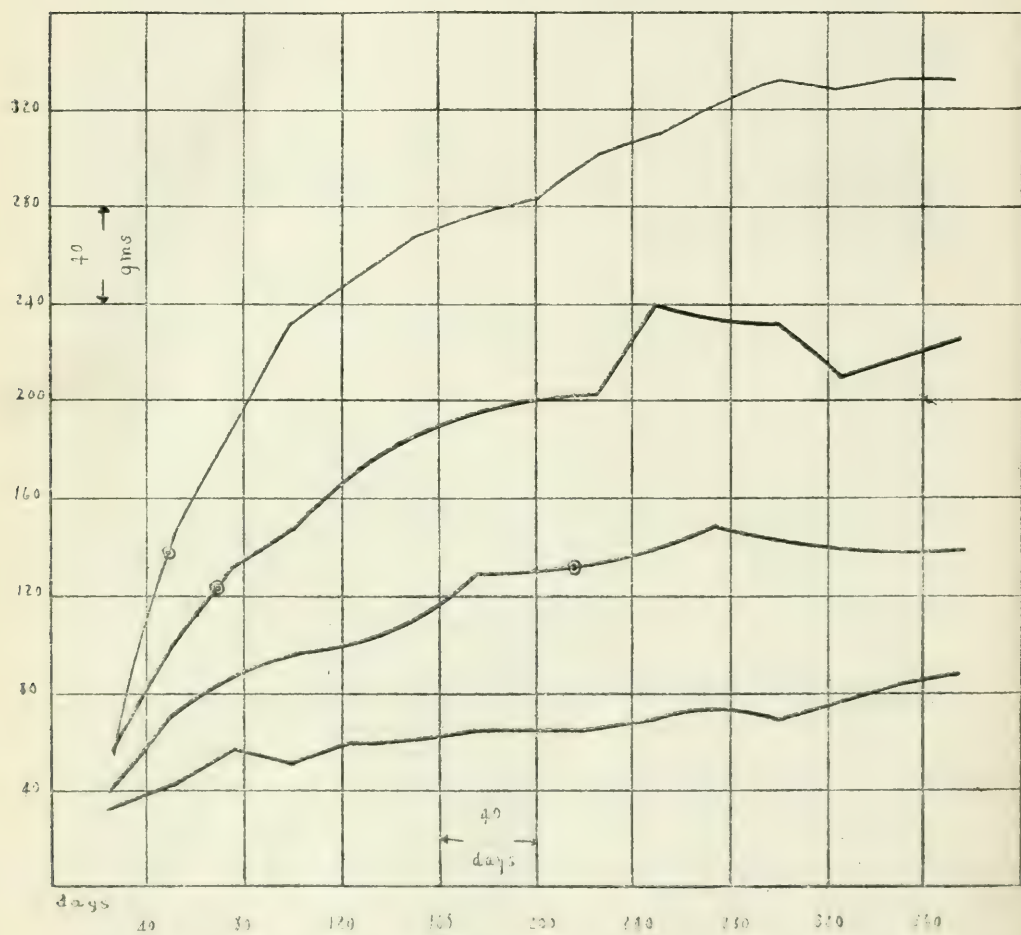


FIGURE 1.

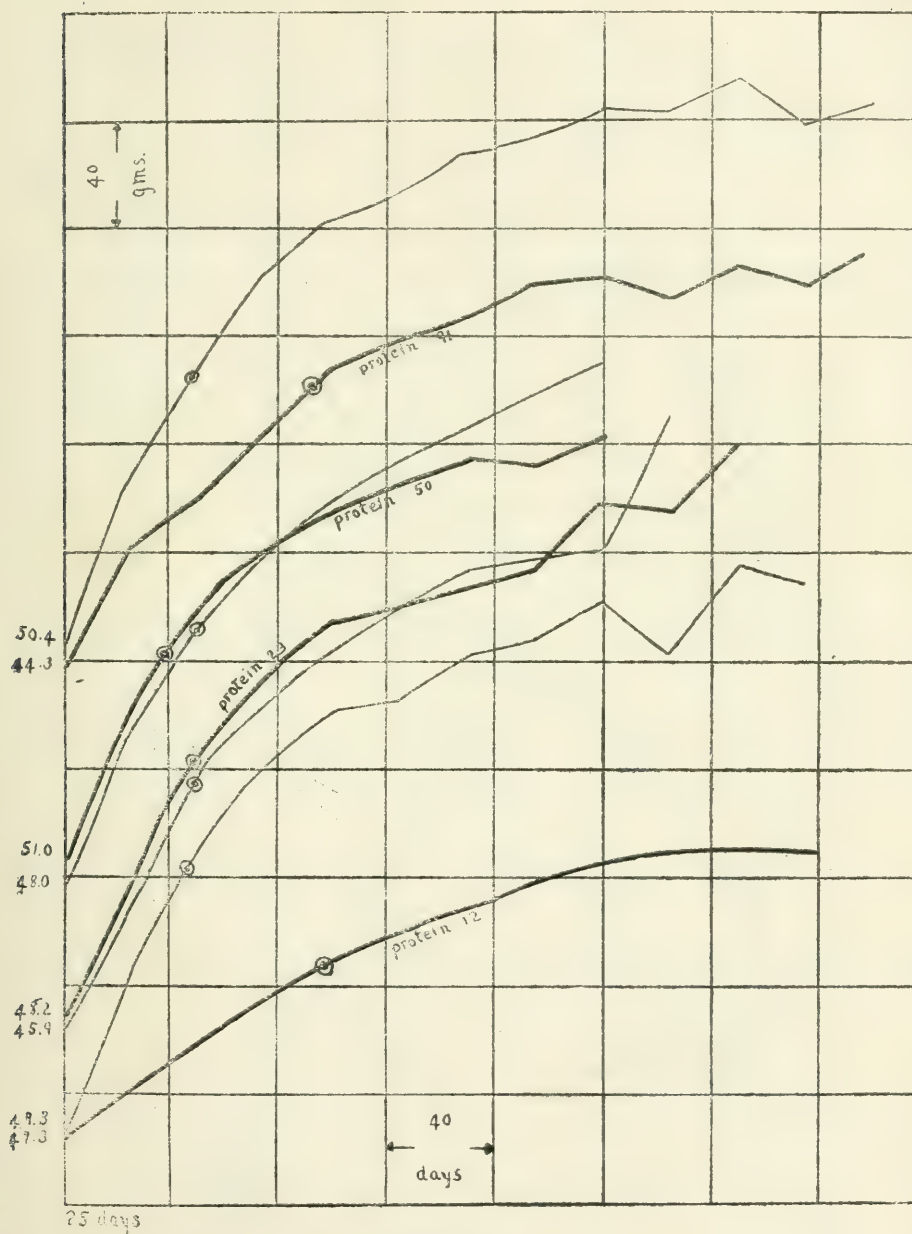


FIGURE 2.

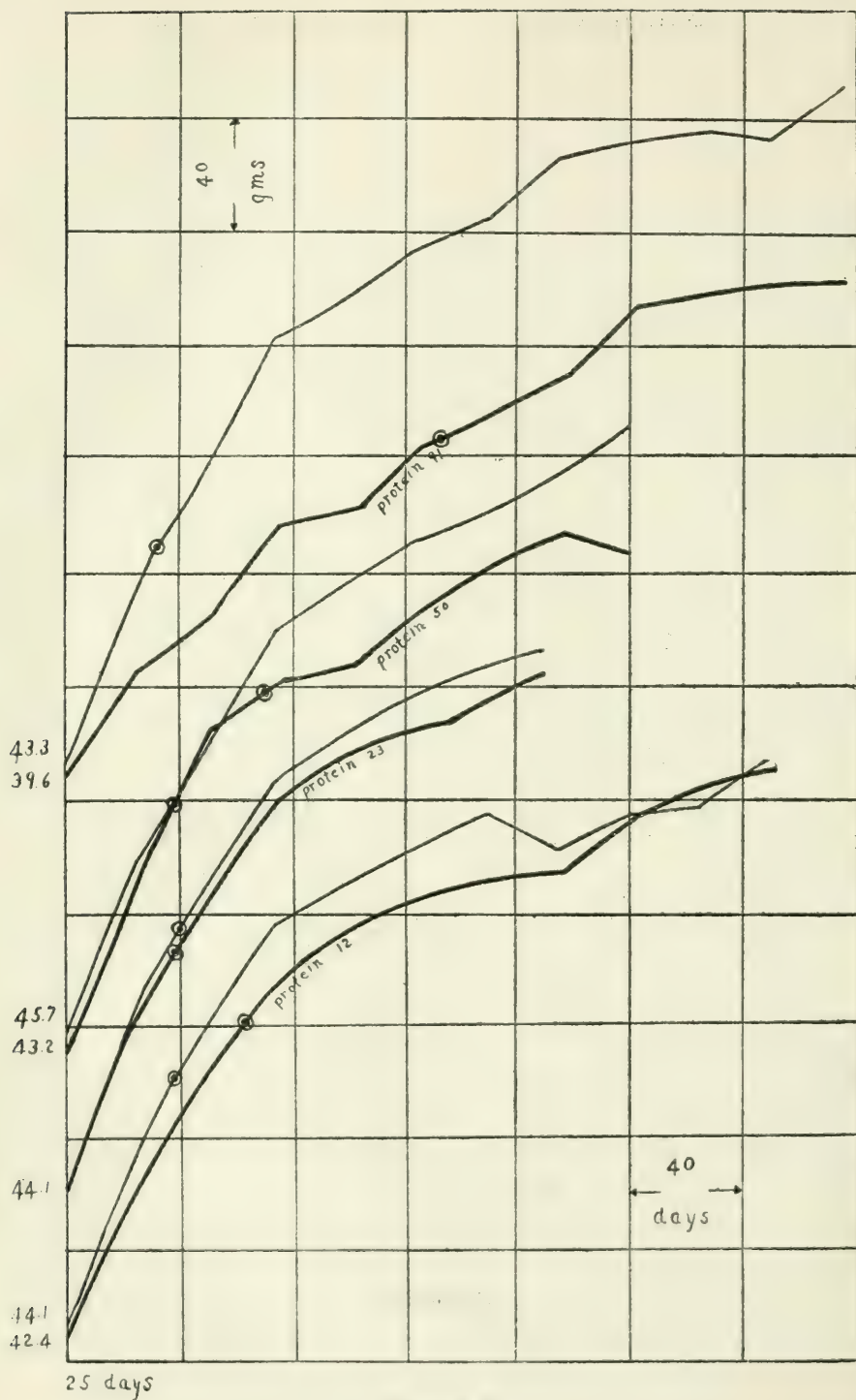


FIGURE 3.

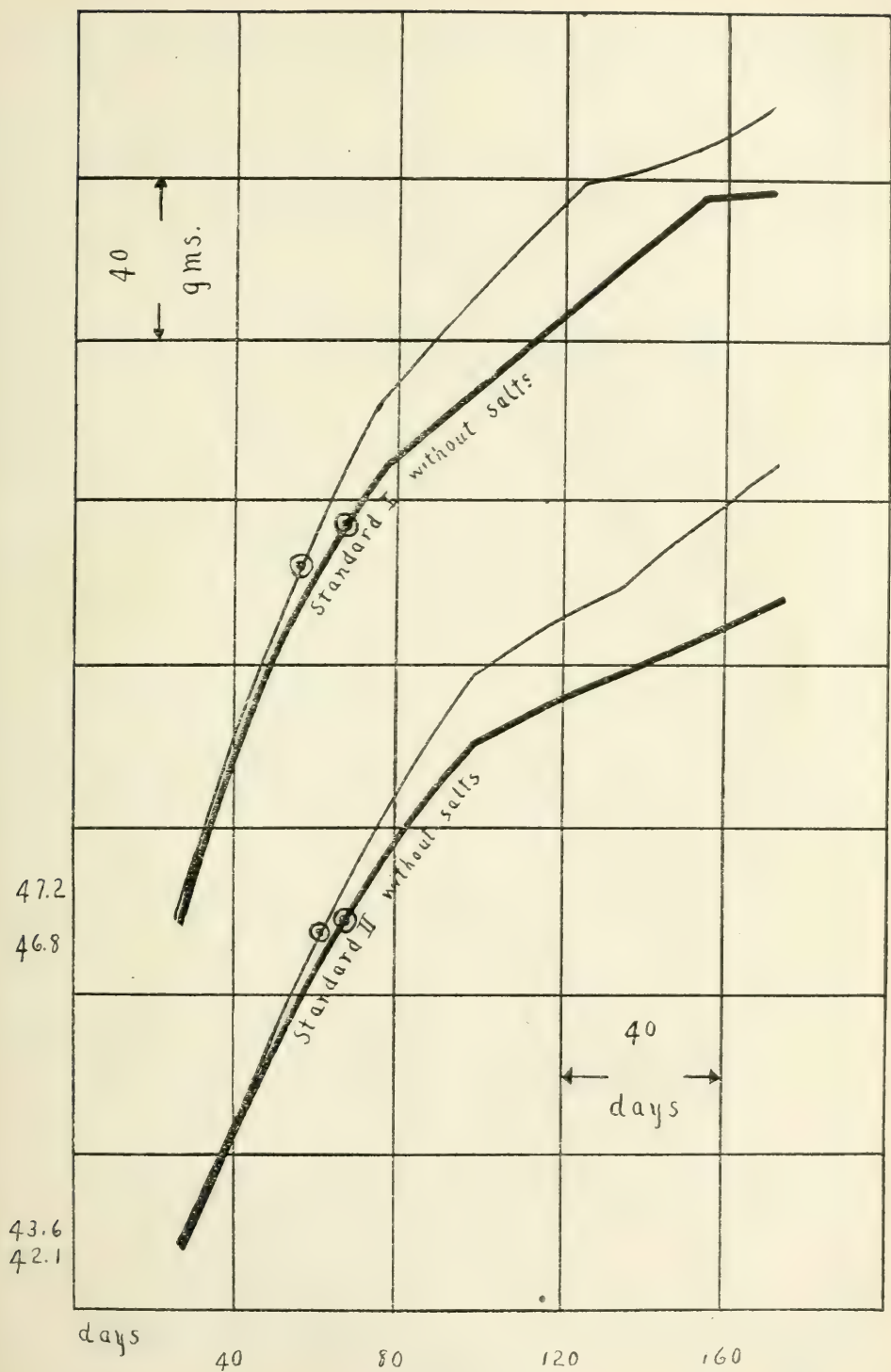


FIGURE 4.

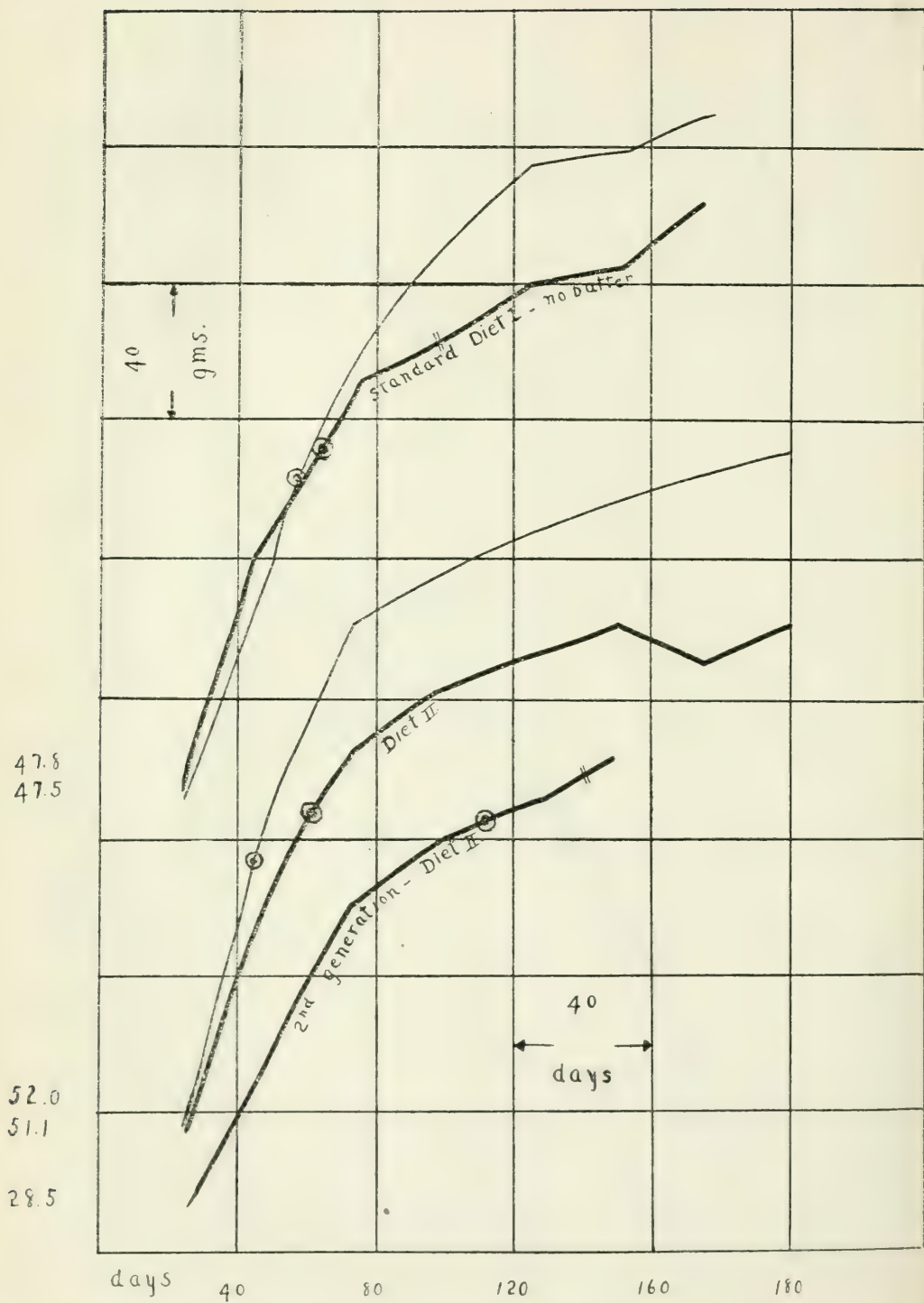


FIGURE 5.

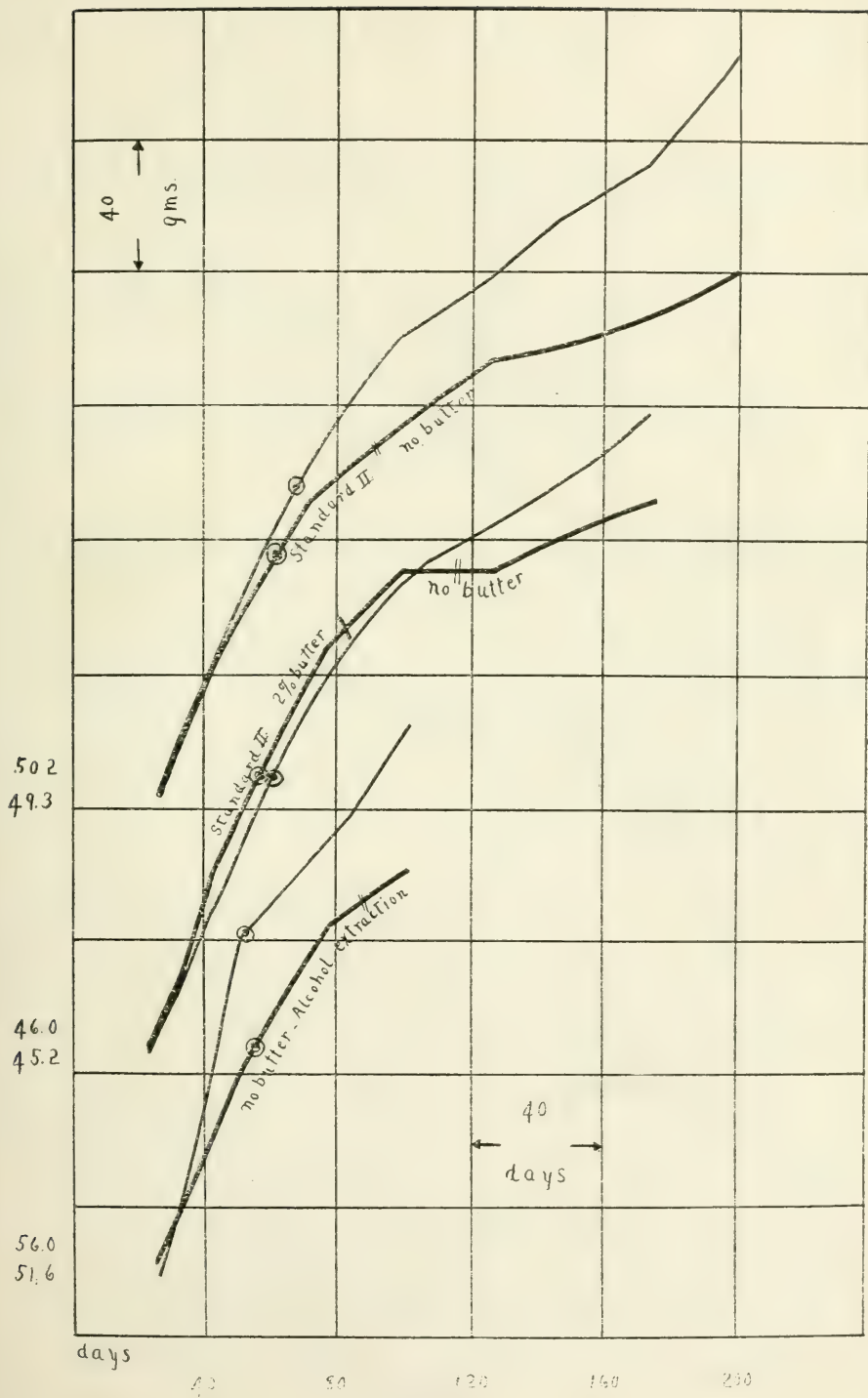


FIGURE 6.

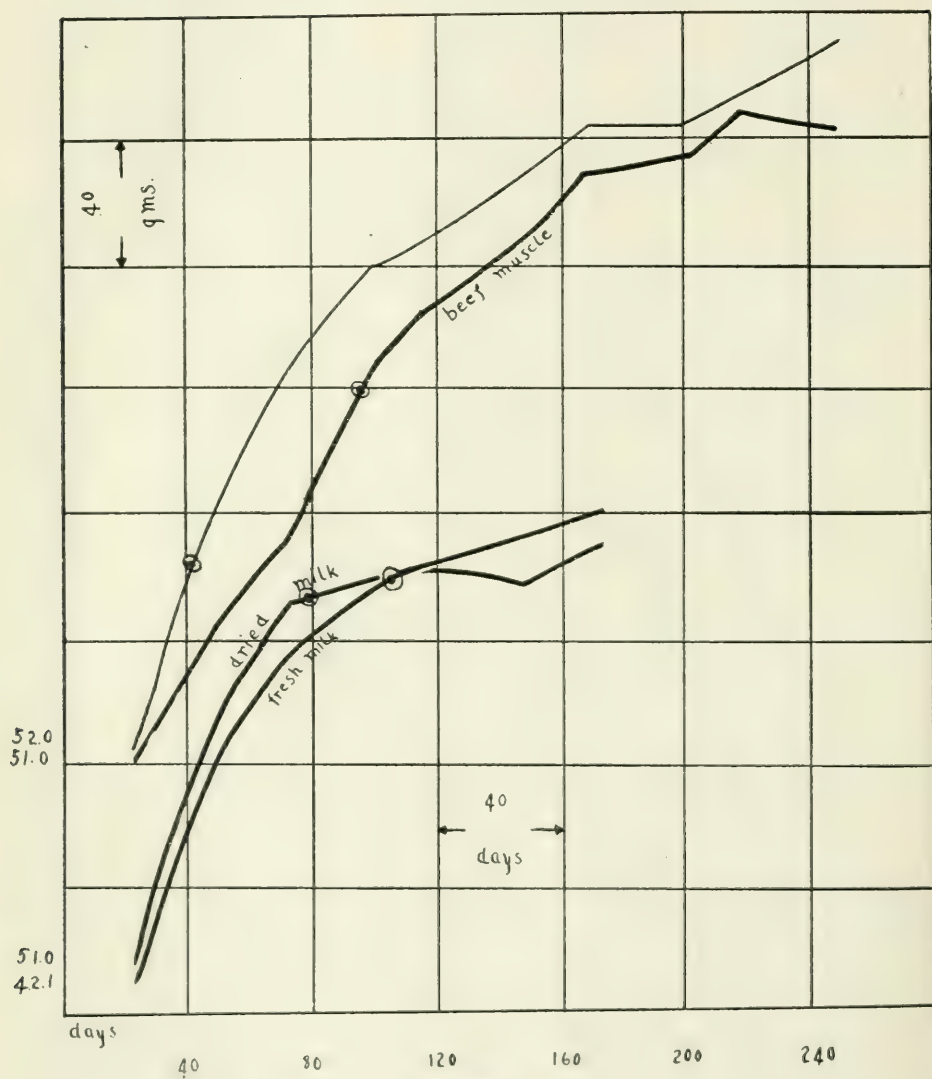


FIGURE 7.

25

NON-SURGICAL DUODENO-BILIARY DRAINAGE IN DIABETES AND HYPERTENSION CASES.

BY

JULIUS J. SELMAN, M. D.,

The Physiatrie Institute, Morristown, N. J.

HARRISON S. MARTLAND, M. D.

Pathological Laboratory, Newark City Hospital, Newark, N. J.

AND MARTIN J. SYNNOTT, M. D.,

Montclair, N. J.

The rôle that infections play as etiologic factors in the production of the pancreatic disturbance underlying diabetes has become sufficiently appreciated only recently with the taking of more careful histories. It is particularly suggestive that a number of these patients give histories indicative of gall-bladder or hepatic disease; more give histories of chronic indigestion and other vague symptoms referable to the upper abdomen. It has been pointed out by a series of writers^{1, 1A} that such infections may be carried from the gall-bladder by means of the lymphatics to the glands at the head of the pancreas, producing a lymphangitis, lymphadenitis, and a lymph stasis which later becomes organized and results in chronic pancreatitis.

Mitchell² in a study at the Physiatrie Institute of 116 cases, whose history could be relied upon, found that "of 8 cases in which infection was an immediate antecedent of diabetes, 4 gave histories of jaundice and cholecystitis"; of 43 cases showing "a suggestive relationship between pathology or infection and diabetes, there were 10 cases of liver or gall-bladder disease". Since publication of these results, an examination of an additional 225 cases showed that 27 gave histories of previous liver or gall-bladder disease. Joslin³ reported 20 cases of diabetes following gall-stones. Allen⁴ in a study of pancreatic specimens in 570 cases, chiefly non-diabetic, coming to autopsy found a "significantly high proportion of pancreatic lesions in association with cirrhosis of the liver and gall-stones". Of Wilder's⁵ group of 53 patients

with diabetes who had an interstitial pancreatitis proved by exploratory operation or suggested strongly by the presence of cholecystitis or other inflammatory disease, there were many who were operated on because of gall-bladder disease or other abdominal disorders.

For this reason and realizing the close anatomical association of the pancreas with the biliary apparatus⁶, a study was undertaken of the biliary secretions of 53 patients under treatment for diabetes in the Physiatrie Institute. At the same time it was desired to test the effect of biliary drainage on (1) the patient's tolerance for food, (2) the downward progress of those who under strict observation and dietary control still appeared to be going down hill. For comparison, three cases of hypertension and one of pancreatitis in the Institute were subjected to the same procedure.

In order to determine the incidence of infection, biliary drainage was done on all patients as a routine measure. The procedure used was the now well-known method of Lyon⁷. This test, which was suggested by the work of Meltzer⁸ and also by the previous work of Doyon⁹ and Oddi¹⁰, presupposes (1) "the sphincter action of the muscle of Oddi, (2) the law of contrary innervation in the contraction of the gall-bladder with the relaxation of the muscle of Oddi, (3) the specific action of magnesium sulphate in the duodenum in initiating the functioning of this law"¹¹. Whether this phenomenon is the result of a "contrary nervous innervation" as Meltzer thought, or of osmosis, or is due to a syphonage of bile stored in the gall-bladder, or to the milking action¹ set up by the duodenal peristalsis, is still a matter of discussion and controversy. Lyon has apparently taken for granted the contraction of the gall-bladder, since Meltzer did not demonstrate this fact in animal experiments. All writers have agreed that magnesium sulphate does relax the papilla and as a result an increased flow of bile is obtained. This was proved experimentally by McWhorter¹². However, some of the clinical observers, namely Crohn, Reiss and Radin¹³, Auster and Crohn¹⁴, Bassler, Luckett and Lutz¹⁵, and Einhorn¹⁶ disagree with Lyon in his supposition that there is a contraction of the gall-bladder following the use of magnesium sulphate solution. At laparotomy, with the duodenal tube in position, injection of magnesium sulphate solution was not followed

by visible contraction of the gall-bladder. In addition to this, Auster and Crohn¹⁴ injected a solution of methylene blue into the gall-bladders of 8 anesthetized dogs, then irrigated the duodenal mucosa in the region of and including the papilla of Vater with magnesium sulphate, and in only one was the methylene blue returned. Smithies, Karshner and Olson¹⁷ point out that "when magnesium sulphate is injected into the duodenum of a patient under anesthesia, it should not be expected that physiologic function is normal" and quote the observations of Sachs¹⁸, Lesner¹⁹ and Friedenwald who found that "in incompletely anesthetized individuals and in dogs whose duodena have been segregated, local introduction of hyperisotonic solutions of magnesium sulphate, with subsequent early withdrawal, produces a definite, visible dilation of the viscus, contraction of the gall-bladder and of the bile ducts, with outpouring of bladder and liver bile". As to the efficacy of the method in the bacteriological study of the biliary tract and pancreas, Whipple¹¹ found that "in about 50% of the cases, one or more varieties of bacteria found in the preoperative duodenal bile were present in the gall-bladder bile or gall-bladder tissue at operation". Lyon, Bartle and Ellison^{20, 21} recently quoted their experience in 400 cases to prove their former contentions. The controversy which has arisen can be easily recognized by a somewhat incomplete perusal of the literature²² already printed. It is not our purpose to enter into the controversy, however, as it suffices that the method can be used to study biliary secretions both bacteriologically and microscopically.

The following routine was used in the examination of all specimens removed by biliary drainage:

After estimating the quantity of A, B and C biles ("A" bile representing common duct bile, "B" bile representing gall-bladder bile, and "C" bile representing hepatic duct and liver bile, according to Lyon's view) and allowing 1 cc. of B bile to aspirate into a 200 cc. Erlenmeyer flask containing 100 cc. of gelatin colloidal broth for culture purposes, the specimens and culture flasks were sent direct to one of us (HSM) for examination, marked with the patient's name but containing no clinical data. Throughout the entire series at no time was the laboratory worker acquainted with the clinical history or findings; this we believe greatly increases the value of the interpretations. The problem for the laboratory worker was to state whether the bile in question was infected or clear, according to the gross examination of the bile for

turbidity, flocculi and mucus; the microscopic examination for the presence of pus, blood, epithelium and crystals; the bacteriologic examination to determine whether the flora was normal or increased, the presence of massed bacteria and colony formation, the morphology of the micro-organisms present in hanging drop and direct smear, and their complete identification by cultural methods.

All specimens were examined as soon as possible after removal. The gross and microscopic examination of the bile specimens must be made directly after removal or within four hours time, as we found that rapid growth of micro-organisms even at room temperature will make it impossible to interpret whether the bacterial flora is increased or normal. Changes in color and turbidity also occur after standing, the change in turbidity being due to chemical change in the bile with precipitation of salts or to bacterial growth, or both. Allowing the specimens to remain overnight in an ice-chest is a worthless procedure, the bile becoming unfit for cytological examination. As the interpretation between infected and clear bile in low-grade chronic infections rests upon the estimation of very fine variations from the normal in the turbidity, the amount of mucus present, the number of leucocytes present, the presence of increased numbers of bacteria, in massed or colony formation, etc., it is obvious why specimens should be examined directly or within four hours after removal.

GROSS EXAMINATION

The color of the bile specimens was first noted. Usually the A bile varies from a watery to greenish yellow color, the B bile from greenish yellow, green brown, green-pea, dark green to black, and the C bile from golden brown to lemon color, provided the so-called play of colors takes place. The color, however, afforded no judgment of the presence of infection.

The reaction of the specimens to litmus was next found. Occasionally turbid specimens will be encountered, which are markedly acid in reaction, the turbidity in these specimens being due to an admixture of the bile with acid gastric juice passing across the duodenum and meeting the flowing bile. Such specimens are worthless for cytological examination and for estimation of bacteria, since they are contaminated.

The specimens showing an alkaline, neutral or slightly acid reaction to litmus were then examined for turbidity and the degree noted (1 to 5). The presence of turbidity in slightly acid, alkaline or neutral bile, directly or within a short time after removal (it being assured that the technique of obtaining specimens was correct) was the first evidence in the examination that we had in favor of possible infection.

The presence of microscopic mucus, clear or bile stained; flocculi; pus or blood was then noted. The presence of any of these strongly favored the final impression that such a bile was infected.

The viscosity of the bile was then noted. The A bile is usually watery, the B bile ropy, and the C bile limpid. The viscosity, however,

does not seem to be an important point in the determination of infection in these low-grade cases.

From the gross examination of the bile a general impression of infection could often be made, based mainly upon turbidity, presence of flocculi, mucus or frank pus.

MICROSCOPIC EXAMINATION

Cover-glass, wet preparations of the bile were made by pipetting off a sample and catching small masses of mucus in the pipette if possible. These were examined with low and high dry objectives for the presence first of leucocytes. Normal bile should contain few or no leucocytes. Leucocytes occurring in any numbers and especially in clumps were regarded as very positive findings in favor of infection. The following data were noted: (1) the presence of clear or bile-stained mucus; (2) the presence of epithelium, especially cuboidal, low and high columnar; (3) the presence of lecithin, cholesterol, glycocoll, bile salts and soap needles. In the low-grade infections encountered in this investigation epithelium and crystals were rarely seen in any quantity.

The microscopic examination of the bile can also be made from centrifugalized specimens as far as the search for leucocytes, epithelium, etc., is concerned; these will not do, however, for the determination of the bacterial content, since the bacteria become packed and give misleading interpretations.

Hanging drop preparations and stained smears by Gram's method were then prepared to determine whether the bacteria were increased in number over normal and to study their morphology. The originators of this method make no claim of obtaining sterile specimens by their method and consequently normal bile obtained in this way will contain many free bacteria, which often grow profusely on culture. Normal specimens should not, when examined shortly after removal, show large numbers of micro-organisms, nor particularly should they show organisms occurring in massed or colony formation. The impression of an increased bacterial flora is really formed from the above picture. The hanging drop preparation also gives us information as to the morphology of the organisms present, the presence or absence of long or short bacilli, their motility or non-motility, the presence of cocci, etc. Further partial identification is made with the Gram stain.

BACTERIOLOGICAL EXAMINATION

The broth flasks containing a culture of the B bile were placed in the incubator over night. The next day they were examined by hanging drop and direct smears by Gram's method and their general morphological characteristics determined. Plain agar plates were poured with varying dilutions according to the profuseness of growth in the broth flasks. After 24 hours incubation the approximate number of colonies on the agar plates were roughly counted. Subcultures on suitable media were then made for complete identification of bacteria. In infected

biles there was usually a profuse and very rapid growth of the infecting organisms in the original broth flask, in contra-distinction to the free biles where the growth was much slower.

In summarizing, we found the following criteria the most important in the laboratory determination of infected bile obtained by the Lyon method:

(1) The bile must be examined as soon as possible after removal, preferably within an hour, not later than 4 hours. Examination after preservation in ice-chest was useless.

(2) The important observations to be noted in the gross examination of the bile were the reaction; the turbidity, due to presence of flocculi, mucus, cells, and bacteria; the presence of clear or bile-stained mucus, etc.

(3) The important data in the microscopic examination of the bile were the cytology, namely, the finding of pus cells, free or in clumps; the presence of mucus, clear or bile-stained; the presence of epithelium from the gall-bladder and ducts, and the presence in hanging-drop preparations of an increased bacterial flora, manifested by numerous free bacteria, bacteria occurring especially in clumps and colony formation, the morphology of the micro-organisms present and their behavior with reference to motility and Gram's stain.

(4) The important data in the bacteriological examination used for complete identification of organisms present were the rapidity with which growth occurs in the colloidal broth flasks and the number of colonies present in subcultures on agar plates.

We did not attempt in this study to prove or disprove the statement that by the Lyon method bile can be segregated with any degree of accuracy from the different parts of the biliary tract, namely, common duct, gall-bladder and hepatic duct bile; the main fact that we wish to establish is that in a few cases of diabetes there is definite evidence of infection of the biliary tract above the ampulla.

The colloidal gelatin broth used in these studies was made according to directions given us by Dr. John A. Kolmer²⁸ of Philadelphia, and is a modified form of the broth devised by Dr. Huntoon and recommended as a rapid and efficient general medium for field-work during the late war.

TABLE I.
Cases of Diabetes Studied.

Case No.	Age at Admission	Date of Admission	DURATION OF DIABETES				BODY WEIGHT			Initial Diet Gm. Protein, Gm. CH. and Total Calories	Later Diet Protein, CH and Total Cal.	History of Previous Gastric or Biliary Symptoms	Infection in Bile Specimens
			Before Admis- sion		Total	Pounds							
			Yr.	Mo.		Before Dia- betes	At Admis- sion	Final					
									Yr.				
955	60	Nov., 1921	7	..	4	7	4	174	122	30 protein for 3 days...	70-20-1400	Negative	Negative
839	43	Sept., 1921	3	..	7	3	7	148	97	30 protein for 3 weeks...	40-5-700	Negative	Negative
60	30	Oct., 1919	2	6	29	4	11	155	140	40-15-400 within 10 days	60-20-1400	Jaundice in 1913	Negative
883	30	Oct., 1921	0	1	5	0	6	148	118	30 protein for 7 days...	65-15-1300	Frequent "bilious attacks" with some nausea and vomiting	Suspected
3	15	Oct., 1915	0	6	76	6	10	100	98	30 protein for 8 days...	50-5-800	Negative	Negative
78	44	Oct., 1919	0	3	29	2	8	174	151	900 cal. for 2 days...	Unweighed	Influenza in April, 1921; one month after had severe jaundice lasting 4 weeks; in summer, 1921, had two attacks of nausea and vomiting	Positive
630	46	Oct., 1921	5	..	5	5	5	155	124	25 protein for 9 days...	50-5-800	Negative	Negative
799	53	Sept., 1921	12	..	6	12	6	160	99	20 protein for 20 days...	60-10-1200	Negative	Negative
1032	50	Nov., 1921	6	..	4	6	4	170	120	20 protein for 6 weeks...	40-0-600	Diarrhea for past 2 years	Negative
845	35	Sept., 1921	4	..	6	4	6	198	136	30 protein for 2 weeks...	65-15-1200	Negative	Negative
840	63	Sept., 1921	5	..	7	5	7	175	117	30 protein for 1 month...	70-20-1700	Negative	Negative
108	62	Dec., 1918	3	..	39	6	3	154	120	50 protein for 2 days...	Unweighed	History unreliable	Suspected
131	51	Mar., 1921	0	5	12	1	5	170	118	35 protein for 5 weeks...	65-15-1500	Negative	Negative
334	29	Sept., 1920	5	..	17	6	5	165	162	40 protein for 1 day...	Unweighed	Negative	Negative
1039	30	Nov., 1921	0	5	4	0	9	185	133	30 protein for 4 weeks...	60-15-1300	Pain on right side of abdomen just above umbilicus; some nausea	Positive
54	40	Sept., 1919	1	..	30	3	6	150	120	35 protein, 5 CH and 400 cal. for 2 months	50-5-1000	Negative	Negative
24	27	Jan., 1918	5	..	50	9	2	135	105	Fasted 4 days, then 30 protein for 17 days...	50-10-1000	Negative	Negative
762	43	Nov., 1915	14	9	76	21	1	200	165	30 protein for 4 days...	60-10	In 1901 patient had catarrhal jaundice for 8 weeks; was not confined to bed. In past 2 years has had occasional attacks of jaundice	Negative
823	25	Aug., 1921	0	11	8	1	7	122	89	25 protein for 6 days...	65-20-1600	Negative	Negative
931	41	Feb., 1922	3	8	1	3	9	150	105	20 protein for 1 month...	20 protein	Jaundice 8 years ago...	Negative
929	62	Jan., 1922	10	..	2	10	2	160	120	30 protein for 7 days...	50-5-500	Negative	Negative
938	50	Jan., 1922	20	..	2	20	2	200	166	40 protein, 5 CH for 5 days	70-35-1600	Negative	Negative
1044	47	Nov., 1921	3	..	4	3	4	168	135	30 protein for 4 weeks...	55-15-1300	Negative	Negative
26	25	Dec., 1921	5	..	3	5	3	148	112	30 protein...	30-10-1000	Negative	Negative
1073	47	Dec., 1921	1	..	3	1	3	170	152	1000 cal. for 3 days...	65-20	Epigastric pain with nausea and vomiting; no jaundice; diagnosed as pancreatic calculi	Negative
1047	48	Dec., 1921	3	..	3	178	115	35 protein, 5 CH for 2 weeks	65-20-1500	Jaundice 30 years ago; recovered in 1 week	Negative
1049	49	Dec., 1921	3	..	3	170	96	30 protein for 2 weeks...	45-5-900	Negative	Negative
1048	45	Dec., 1921	3	..	3	195	152	40 protein for 8 days...	65-20-1300	Negative	Negative
1038	46	Nov., 1921	6	..	4	6	4	195	140	40 protein for 8 days...	65-20-1300	Negative	Negative

*Note—The day after drainage patient had an attack of violent pain below the right border of the ribs, accompanied by jaundice and fever.

TABLE I. (continued)

Case No.	Age at Admission	Date of Admission	DURATION OF DIABETES				BODY WEIGHT			Initial Diet Gm. Protein, Gm. CH, and Total Calories	Later Diet Protein, CH and Total Cal.	History of Previous Gastro or Biliary Symptoms	Infection in Bile Specimens	
			Before Admis- sion		After Admis- sion	Total	Pounds							
			Yr.	Mo.			Yr.	Mo.	Before Dia- betes					At Admis- sion
1029	41	Nov., 1921	0	5	5	0	9	182	126	115	30 protein for 3 weeks..	65-15-1600	Jaundice in childhood.....	Negative
1033	56	Nov., 1921	0	2	4	0	6	155	120	108	20 protein for 5 weeks..	40- 5-900	Negative.....	1. Suspected 2. Negative
1003	40	Oct., 1921	5	..	5	5	5	168	120	120	30 protein for 16 days..	50-10-1200	Jaundice.....	Negative
1030	49	Nov., 1921	0	6	4	0	10	233	160	158	30 protein, 10 CH for 1 day	90-45	Negative.....	Negative
887	25	Oct., 1921	1	..	5	1	5	131	110	101	30 protein for 18 days...	55-15-1300	Negative.....	Negative
951	50	Oct., 1921	2	..	5	2	5	195	133	127	30 protein for 3 days...	75-25-1900	Cholecystectomy for gall-stones 18 years ago	Negative
680	30	Aug., 1921	1	..	7	1	7	143	115	81	Uncontrollable.....	..	Jaundice 11 years ago, followed by colic, several attacks of jaundice since	Negative
874	55	Sept., 1921	7	..	6	7	6	200	134	110	30 protein for 16 days..	30-10-900	Negative.....	Negative
1012	55	Nov., 1921	9	..	5	9	5	160	127	128	40 protein, 10 CH for 2 weeks	65-15-1200	Negative.....	Negative
1018	37	Nov., 1921	0	6	4	0	10	210	210	205	40 protein, 5 CH for 3 days	80-20	Negative.....	Negative
1009	17	Oct., 1921	0	3	5	0	8	115	106	102	30 protein for 7 days...	60-15-1400	Several attacks of gall-stone colic with jaundice from 1900 to 1904; then none until 1912, when they commenced again	Negative Positive
291	49	June, 1920	6	..	21	7	9	170	115	102	30 protein, 10 CH for 9 days	50-10-1000	Negative.....	Negative
878	47	Oct., 1921	2	..	5	2	5	126	92	74	30 protein for 10 days; then alternate fast day with 20 protein for 3 weeks	60-10-1400	Negative.....	Negative
932	40	Oct., 1921	2	..	5	2	5	215	123	100	30 protein for 2 weeks...	65-15-1700	Negative.....	Negative
963	39	Nov., 1921	3	..	4	3	4	174	140	135	40 protein for 5 days...	70-20-1400	Negative.....	Negative
965	57	Nov., 1921	6	..	4	6	4	153	123	119	35 protein, 5 CH for 6 days	65-70-1600	Negative.....	Negative
1086	50	Feb., 1922	1	5	1	1	6	172	111	109	30 protein for 3 days...	55-10-1200	Vague pains in gall-bladder re- gion, radiating to right axilla and shoulder; jaundice	1. Suspected 2. Negative
1100	53	Feb., 1922	0	8	1	1	0	181	126	125	30 protein for 12 days..	30 protein	Negative.....	Negative
1101	24	Feb., 1922	3	11	1	4	..	153	100	72	25 protein for 6 days...	50-5-1000	Jaundice in 1908; chronic in- digestion	Negative
787	43	July, 1921	0	4	9	1	1	229	179	152	30 protein for 14 days...	55-10-1000	"Auto-Intoxication" 2 years ago	Negative
991	43	Jan., 1922	4	6	2	4	8	200	151	147	30 protein for 7 days...	65-15-1400	Negative.....	Negative
914	70	Jan., 1922	0	7	2	0	9	190	147	132	40 protein, 5 CH for 5 days	55-20-1100	Negative.....	Negative
940	45	Jan., 1922	6	3	1	6	4	150	117	103	30 protein for 8 days...	45-10-900	Negative.....	Negative
934	48	Jan., 1922	9	..	2	9	2	7	101	97	30 protein for 3 days...	70-25-1700	Negative.....	Negative
1097	50	Feb., 1922	0	7	1	1	0	168	129	123	30 protein for 9 days...	60-30-1300	Negative.....	Negative

TABLE I A. *Cases Other Than Diabetes Studied.*

Case No.	Diagnosis	Age at Admission Yrs.	Duration of Illness Yrs.	Initial Diet	Later Diet	History of Previous Gastric or Biliary Symptoms	Infection in Bile Specimens
957	Hypertension..... Arteriosclerosis Chronic Nephritis	55	1	70 protein, 30 CH, salt-free.	Unweighed, low calory, salt-free.	Gallstone colic, jaundice and fever in 1914. Cholecystectomy in the same year	Positive
1041	Hypertension..... Chronic Nephritis	51	1	Unweighed; salt-free.....	Unweighed; salt-free.....	Attacks of jaundice with fever.....	Negative
1083	Chronic Pancreatitis	21	3	Unrestricted.....	Unrestricted.....	Indigestion throughout life; influenza 3 years ago, followed by very frequent attacks of diarrhea, cramps, jaundice, and severe pain in epigastrium	Suspected
2009	Hypertension.....	52	3	Unweighed, salt-free.....	Unweighed, salt-free.....	Flatulence, indigestion, and heaviness in epigastrium for 10 years	Negative

It is prepared as follows:

Gelatin Broth (Colloidal) Huntton

- | | | |
|-----|-------------------------|-----------|
| (a) | Ground beef heart | 500 grams |
| | Peptone | 10 grams |
| | Salt | 5 grams |
| | Gelatine | 10 grams |
| | Water, tap..... | 1000 cc. |
- (b) Add one egg, shell included, slightly beaten.
 - (c) Mix well these ingredients and if time permits place in ice-chest over night.
 - (d) Heat the mixture to 68° C., or until the meat turns brown. Heat over open gas stove or water-bath; if over open flame constantly stir using agate-ware long spoon.
 - (e) Place in Arnold sterilizer for one hour from boiling-point.
 - (f) With glass rod, carefully remove clots from side of container.
 - (g) Replace in the Arnold for one and one half hours or until broth separates and the coagulum sinks to the bottom of the container. Strain off meat by means of a fine wire sieve.
 - (h) Titrate to 0.5 plus using phenolphthalein, then add 0.1 per cent. glucose.
 - (i) After adding the required normal sodium hydrate, replace the container in the Arnold for 20 minutes to throw down the phosphates.
 - (j) When entirely cold, fat and phosphates may be removed by means of a filter made of glass wool and asbestos wool. If the broth is filtered while hot the fat may be removed by means of a separatory funnel.
 - (k) The broth must not come in contact with any vegetable fiber.
 - (l) The sterilization is important (heating should not be greater than 100° C.) and is best done with the Arnold sterilizer. If the broth is in the tubes the sterilization should be for 30 minutes after boiling begins, for three successive days. If larger containers are used the time must be longer in proportion. After the last sterilization, the broth is held under observation for five days for sterility before use.
 - (m) Each batch of media is tested with a culture of streptococcus and pneumococcus and rejected unless luxuriant growths are obtained in 48 hours.

Of 57 diabetic and other patients (Tables 1 and 1A) upon whom the procedure was used there was a positive history of gastric or biliary symptoms in 20 cases. Of these 20, there were 3 cases (291, 951, 78) in which a positive diagnosis could be made; in 3 cases (883, 1083, 108) a diagnosis of suspected infection was made. Two other cases showed suspected infection at first examination but were negative at the second test. Of the 6 cases specially studied, one (957) had hypertension without diabetes and had had a cholecystectomy done in 1914, one (1083) had chronic pancreatitis, the other four (291, 883, 78, 108) were cases of frank diabetes. In only one case (108) was the diagnosis of suspected infection made where no positive history of symptoms could be obtained.

It may be well to state that we were able to get a growth of some sort of organism in almost every case if the cultures were allowed to incubate longer than 24 hours, but gross and microscopic examination did not meet the criteria as laid down previously. The results of the microscopic and bacteriologic studies on those cases in which a diagnosis of positive or suspected infection could be made are given in Table II.

Case 1039. — Male; age 28 years; diabetes of 10 months' duration.

The family history was negative. He had measles, mumps, whooping cough, and several peritonsillar abscesses in childhood. During the past few years there have been several attacks of pain on the right side of the abdomen just above the umbilicus; these attacks were accompanied with nausea and vomiting. He had a "cold" in April, 1921, at which time glycosuria was found; however, frank symptoms of diabetes were already present. Physical examination was negative.

On Nov. 29, 1921, after the first biliary drainage the A, B and C biles were all slightly turbid. The A and B biles showed a few flocculi and a small amount of mucus; microscopic examination showed a few free leucocytes, a small amount of mucus, and numerous bacteria, free, in clumps and slight colony formation. Cultures showed the predominating organisms to be *Staphylococcus aureus* and *B. subtilis*. There is definite infection of A and B biles and possibly of the C bile.

On Dec. 7, 1921, after a 2nd biliary drainage the A and B biles were very turbid, the A bile showing a small amount of clear mucus; microscopic examination showed a small amount of free mucus and a few free leucocytes in both A and B biles; the bacterial flora was slightly increased, showing massed bacteria and a few colonies in A bile. The C bile was not obtained. Cultures showed the predominating organisms to be *Staphylococcus aureus* and *B. subtilis*. There is definite infection of A and B biles.

TABLE II.

Summary of gross, microscopic and bacteriological findings in six cases showing infection of biliary tract.

Case No.	GROSS EXAMINATION										MICROSCOPIC EXAMINATION													BACTERIAL EXAMINATION																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
	Specimen	Impression of gross examination										Cells			E. ITH.			Crystals				Micro-Organisms						Impression of microscopic examination	Organisms identified in cultures of Bile																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								
		Color	Turbid	Reaction	Clear mucus	Bile st. mucus	Floculi	Gross pus	Gross blood	Watery	Limpid	W. B. C. free	W. B. C. clumps	Erythrocytes	Clear mucus	Bile st. mucus	Cuboidal	Low columnar	High columnar	Bile stained	Lecithin	Cholesterol	Glycerol		Bile salts	Soap needles	Yeasts			Flora normal	Flora increased	Free bacteria	Massed and colonies	Bacilli long	Bacilli short	Cocci in chains	Cocci in clumps	Cocci diplo	Other organisms																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
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On Jan. 24, 1922, after a 3rd biliary drainage, all specimens were clear and showed no gross mucus, etc.; microscopic examination still showed a few free leucocytes in A, B and C biles and a small amount of clear mucus in A and B biles; the bacterial flora was slightly increased and the cultures showed the predominating organisms to be *Staphylococcus aureus* and *B. subtilis*. The bile was apparently clearing under biliary drainage.

On Jan. 30, 1922, after a 4th biliary drainage all specimens were normal on gross examination; microscopic examination showed no leucocytes, and the bacterial flora was normal. Cultures showed a predominating *Staphylococcus aureus*; the *B. subtilis* had disappeared, and a few hemolytic streptococci were found for the first time. The A, B and C biles showed no evidence of infection and the infection had apparently cleared up after the previous treatments.

On Feb. 6, 1922, after a 5th biliary drainage the A and B biles have still remained free from evidence of infection.

We regard as the predominating organism in this case the *Staphylococcus aureus*. The *B. subtilis* we regard as a contaminating organism, which was present in small numbers in the duodenum and grew wildly and profusely on broth.

Following the completion of each drainage, 250 cc. of a 1-4000 Silvol solution was injected into the duodenum and left there.

It is of interest to note that the day after the drainage of January 30, the plasma sugar was 115 mg. per 100 cc., the lowest it had ever been. No special significance is attached to this, since the plasma sugar after the drainage of February 6 was 140 mg. per 100 cc. Even though microscopically the infection had cleared, we cannot be certain as to the final result. Future progress of this case will be interesting as to duration of life and tolerance for increased amounts of food. It did appear, however, that the patient was able to tolerate larger diets with lower plasma sugars than on admission, at which time his case was looked upon as being somewhat stubborn.

Case 78. — Male; age 46 years; diabetes for 2½ years.

The significant facts in the history were that a maternal aunt died of diabetes and nephritis; a cousin has diabetes at present. The patient had measles, chicken-pox, and diphtheria in childhood. He thought himself perfectly healthy up to July 3, 1919, when glycosuria was found during a life insurance examination. On restriction of gross carbohydrate, glycosuria disappeared, but appeared again after injudicious use of the highest carbohydrate foods. He was able to continue on an unweighed diet with restriction of high carbohydrate food and with normal plasma sugars until April 1921, when he had influenza, followed shortly after by a severe jaundice which lasted 4 weeks.

After this attack his plasma sugars had a tendency to run consistently higher, from 146 to 203 mg. per 100 cc. while living on practically the same diet. There was no glycosuria.

On Nov. 16, 1921, after the 1st biliary drainage the A, B and C biles were all slightly turbid, the A and B biles containing a small amount of mucus and a few flocculi. Microscopic examination showed free leucocytes and mucus in the A and B biles. The bacterial flora in all specimens was slightly increased, massed and colony formation being observed in the A and B biles. The predominating organism on culture was *B. coli* with a few hemolytic streptococci. The A and B biles were considered infected.

On Feb. 18, 1922, the 2nd biliary drainage gave the same results as the first examination, and the C bile showed doubtful evidence of infection. *B. coli* and *Streptococcus hemolyticus* were found in cultures.

On Feb. 26, 1922, after the 3rd biliary drainage the same results were obtained, with possible infection of C bile. *B. coli* was the predominating organism found in cultures.

On Mar. 5, 1922, after the 4th biliary drainage A, B and C biles were still slightly turbid and showed a small amount of mucus. Microscopic examination showed a few leucocytes in all, with an increased bacterial flora exhibiting massed and colony formation. *B. coli* and a hemolytic streptococcus were the predominating organisms on culture. The A, B and C biles were regarded as showing definite evidence of infection.

After each one of these drainages 250 cc. of a 2 per cent. solution of sodium sulphate was left in the duodenum. During the period of drainage there has been no evident remission in the degree of infection present.

In this case the indications are, of course, for more intensive treatment. The drainages must be given at more frequent intervals, and supplemented by other treatment if the Lyon method is to have a fair trial as a therapeutic measure. If the infection proves to be so stubborn that it can not be controlled by medical measures, we must perhaps look to surgical intervention as our only means of combatting what appears to be downward progress even though the patient has been under constant observation and dietary control.

Case 291. — Female; age 49 years; diabetes for 7½ years.

The family history revealed that a sister has diabetes at present. The patient had measles at 3 years. From 1900 to 1904, she had six or eight attacks of pain in the gall-bladder region radiating to the scapula; these attacks lasted from a few hours to two or three days. The attacks were accompanied by jaundice. She became free from these attacks until 1912, when they again commenced. The present illness began in 1914 with frank symptoms of diabetes. At the same time she was having pain in the gall-bladder region. Examination of urine showed the presence of glycosuria. Gross carbohydrate was restricted, but she had glycosuria, in varying degrees, until admission

to the Institute (June, 1920). She had lost 40 pounds in weight. The physical examination was essentially negative except for the emaciation incident to the diabetes.

On December 17, 1921, the first biliary drainage was done; the A, B and C biles were all definitely turbid and showed flocculi and mucus present. Microscopic examination showed free leucocytes and pus cells in clumps; mucus was present in all specimens. The bacterial flora was definitely increased, with massed and colony formation. Cultures showed the predominating organism to be *B. coli* and a few *Staphylococcus aureus*. The A, B and C biles were interpreted as definitely infected.

On February 25, 1921, the second biliary drainage was done, showing practically the same findings as the first. *B. coli* was the predominating organism present.

On March 11, 1921, a third biliary drainage showed the A and B biles still infected with *B. coli* to the same degree as before. The C bile was not obtained.

Sodium sulphate solution was also used in this case after each drainage.

Further attempts will be made to clear up this infection by repeated drainages.

Case 883. — Female; 30 years of age; diabetes of 8 months' duration.

The family history was negative. The past history was negative with the exception of "bilious attacks" accompanied by nausea and vomiting which the patient has had for the last five years. The symptoms of diabetes began in August, 1921, and the diagnosis was made in September, 1921. On admission to the Institute on October 17, 1921, she had a moderate glycosuria, which ceased in two days. Three days after the glycosuria had stopped the plasma sugar was 150 mg. per 100 cc.

On November 17, 1921, the first biliary drainage was done. The A and B biles were slightly turbid, the C bile was clear. There were a few flocculi and a small amount of mucus in the A and B biles. Microscopic examination showed a few leucocytes and a small amount of mucus in the A and B biles. The bacterial flora was increased in the A and B biles and normal in the C bile. Massed and colony formation was present in the increased flora. Cultures showed the predominating organisms to be *Streptococcus hemolyticus* and *B. subtilis*. The A and B biles were considered slightly infected. The C bile was considered free.

On February 26, 1922, a second biliary drainage was done. A, B and C biles showed more pronounced evidence of infection than they did at the first drainage. The same organisms were found on culture.

On March 4, 1922, a third biliary drainage was done with the same results, the A, B and C biles all showing evidence of low-grade infection.

Sodium sulphate solution was also used in this case.

Here, again, is a case of diabetes occurring in a young in-

dividual who has a complicating infection of the biliary tract. This infection up to the time of commencing biliary drainage did not interfere with her progress, i.e., she was able to tolerate a fairly liberal diet with normal plasma sugars. After the drainage of March 4, 1922, however, the plasma sugar rose above 200 mg. per 100 cc. and glycosuria soon appeared, so that the diet had to be lowered immediately. This case also called for more intensive drainage than was possible at the time this experimental work was in progress. A drainage every day, or every second day, or even continuous drainage for a period of several days is indicated as essential in the treatment of severe cases.

Case 957. — Female; age 55 years; arterial hypertension for one year.

The family history was negative. The patient had had several attacks of gall-stone colic with fever, jaundice, nausea and vomiting in 1914. Cholecystectomy was done in the same year and she had been practically free from symptoms since that time. The present illness began one year before admission to the Institute, with a ptosis of the left upper lid; this cleared up in 6 months. There was no impairment in strength or use of limbs. She had severe headaches and attacks of palpitation of the heart. Physical examination showed a somewhat obese woman of middle age with a slight ptosis of the left upper eyelid. There was a systolic murmur over the aortic area. The blood pressure was systolic 200, diastolic 110. The peripheral vessels were slightly sclerosed. The abdomen showed a right Rectus surgical scar.

On November 28, 1921, after the 1st biliary drainage the A and B biles were turbid and contained flocculi and clear mucus. The C bile was not obtained. Microscopic examination showed clear and bile-stained mucus and free leucocytes in the A and B biles. The bacterial flora was increased with massed bacteria and considerable colony formation. The predominating organisms after culture were *B. coli* and *Staphylococcus aureus*. *B. pyocyaneus* was present in small numbers. The diagnosis of infected A and B bile was made.

On December 5, 1921, after the 2nd biliary drainage, the A and B biles were quite turbid and showed flocculi and small amounts of mucus. Microscopic examination showed the presence of free leucocytes, a small amount of mucus and occasional epithelial cells from the biliary tract. The bacterial flora was increased in the A and B biles. Massed bacteria and colony formation were observed in them. The C bile was normal. Cultures showed the predominating organism to be *B. coli*, with also many *Staphylococcus aureus* present. The A and B biles were considered infected, the C bile was thought to be normal.

On December 12, 1921, after the 3rd biliary drainage, the A, B and C biles were all quite turbid and contained flocculi and mucus. Microscopic examination showed a few leucocytes and a small amount of

mucus. The bacterial flora was increased, and massed and colony formation was present. The predominating organism on culture was *B. coli*.

Sodium sulphate solution was instilled into the duodenum after each drainage.

Here it is of interest to note that in spite of the fact that the patient had had her gall-bladder removed, she still had a focus of heavy infection in the bile-ducts. This is of significance if the suggestion of MacCallum²⁴ that the combination of a high fat diet, as represented by the slight obesity of the patient, together with a focus of chronic infection may be important etiological factors in the progression of arteriosclerosis.

Case 1083. — Male; age 21 years; chronic pancreatitis.

The significant facts in the family history were that his maternal grandmother died of diabetes, and his mother had glycosuria two years ago, but with slight restriction of carbohydrate food has had no return since. He had measles, mumps, chicken-pox and whooping cough in childhood. Five years ago he was operated on for chronic appendicitis; at the same time he had a double herniotomy performed. He has always had more or less gastric disturbance. Three years ago (Dec. 1918) he had influenza; was up in two weeks; the following day he had an attack of diarrhea accompanied by severe jaundice; the stools were not clay colored but were light in color; he then remained in bed for 5 weeks. Since the first attack, he has had attacks accompanied by the same symptoms about every four to six weeks. During some of these attacks his appetite was ravenous but he had no other symptoms of diabetes. Along with the attacks he observed that he was unable to concentrate on his work and his memory was bad; but these symptoms cleared up when the attack subsided. The patient himself observed that a low diet with restriction of fats caused the attacks to subside very quickly. Previous X-ray examinations of the gastro-intestinal tract including the gall-bladder and ducts were negative. Wassermann tests of the blood and spinal fluid were negative. Physical examination revealed nothing except the scars of the previous operations. Examination of the stools was negative, the patient not being seen during an attack.

While in the hospital, post-absorptive plasma sugars on mixed diet never rose above 128 mg. per 100 cc. A glucose tolerance test with 100 gm. of glucose showed 125 mg. per 100 cc. before giving glucose; in one hour there was 255 mg. per 100 cc.; but at the end of three hours the plasma sugar had dropped to 80 mg. per 100 cc. There was no sugar in any of the urine specimens.

On February 11, 1922, the 1st biliary drainage was done. The A, B and C biles were all markedly turbid. The B and C biles showed a small number of free leucocytes and a small amount of clear mucus. The bacterial flora was increased in these biles and show-

ed massed and colony formation. Cultures showed the predominating organism to be *B. coli*, with a few non-hemolytic streptococci present. The B and C biles were considered infected. On the basis of (1) the significant family history, (2) the history of repeated attacks, suggesting chronic pancreatitis, (3) the lowered tolerance for glucose (the figure 255 mg. per 100 cc. without glycosuria may be explained by a raised renal threshold), and (4) the findings of the biliary drainage, it was decided to refer the patient to a surgeon. At laparotomy, a badly infected gall-bladder and a beginning pancreatitis were found. Cholecystectomy was performed. The details of the pathologic and bacteriologic examination had not been received at the time of writing this article. This operation was advised chiefly to avoid the possible development of a frank diabetes, which is apt to be very dangerous in an individual of this age.

CONCLUSIONS

(1) The negative finding in 49 of the 53 diabetic cases in this series harmonizes with the view that most cases of diabetes are not the result of ascending duct infections extending into the pancreas, but are more probably due to previous attacks of blood-borne infections, such as the acute infectious fevers. This group of cases represent most likely the vestigium of "old burnt-out conflagrations" (Allen).

(2) There is an appreciable number (in our series 6 out of 20 cases) of patients, who have had symptoms of previous affections of the biliary or upper abdominal region who do show evidences of existing infections. In five of these cases (namely, 4 of frank diabetes and 1 of pancreatitis with incipient diabetes) it is important to clear up these infections in order to eliminate one of the main factors contributing toward downward progress. In the case of hypertension, elimination of the focus may destroy a toxic bacterial etiologic factor tending to maintain the hypertension. If medical measures will not suffice, the question is open as to the extent to which prophylactic surgery should be attempted.

(3) The Lyon method is the only available non-surgical diagnostic procedure to determine directly whether or not the biliary system is infected. Where infection is shown to be present, this method offers a mode of therapy, the value of which in certain cases of diabetes remains to be demonstrated by future observation.

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CLINICAL OBSERVATIONS ON TREATMENT AND PROGRESS IN DIABETES.

BY FREDERICK M. ALLEN, M.D. AND JAMES W. SHERRILL, M.D.

From the Physiatric Institute, Morristown, New Jersey.

Several of the early clinicians, notably Frerichs and Külz, published very complete records of their experiences with diabetes, covering their entire series of cases through many years of observation. This was done in the attempt to throw light on the nature, symptoms and progress of the disease, which attracted interest by reason of its mystery. With the passage of time, clinical attention has been directed more to different forms of treatment, and the interest of writers has tended to center in proving the benefits of their particular methods. It speaks none too well for any of these results that, with this shifting of interest, reports of complete clinical experiences have almost vanished from the literature. There may be pleasure and pride in publishing favorable outcomes and the temporary improvements which are sometimes obtained under any treatment, but there is less inclination to record disasters or the fact that a patient once brilliantly benefited has since died. It is now more than ever desirable, however, that clinical writers should present their complete experiences without reserve or bias, for the sake of definite objective comparisons between different plans of treatment, and for the light which can again be shed upon the nature of diabetes.

It is encouraging that several recent authors, especially Joslin¹ in this country and Petró² in Europe, have led the way with full and frank statements of the results obtained under the respective systems of diet which they follow. It is proper that the writer of any textbook or the advocate of any therapeutic method should thus give details of the number of cases treated, their type or severity when received, the resulting control or lack of control of symptoms, the progressiveness or arrest of progressiveness under treatment, and the mortality with its causes. Few persons can fail to observe that the gen-

eral tone and attitude toward diabetes, especially in America and in the British Empire, is more cheerful than formerly, and there must be a question whether the nature of diabetes warrants such cheerfulness, or whether after some temporary benefit the greater number of the cases must decline to a fatal end.

The more optimistic spirit mentioned has been based upon the demonstration that diabetic patients who will co-operate faithfully in diet treatment can, with extremely few exceptions, be rendered free from glycosuria and acidosis and maintained in this condition at least for very long periods. A broad basis of agreement also has been established between all clinicians who deserve to be classed as modern thinkers in this subject, on the two essential and fundamental points concerned: first, that this state of freedom from active diabetic symptoms is possible; and second that (with the possible exception of a small number of cases of extreme severity) it is desirable and beneficial. The agreement of competent judgment on these points, and the absence of any sound evidence against them, suffices to establish them as scientific facts, and the wider extension of treatment based on these principles now requires not proof but merely progapanda. The physician who ignores diabetes in its early or mild forms, or who imposes diet only to the extent of restraining glycosuria within moderate percentages, or who advocates treatment directed to the immediate comfort of the patient instead of to his future safety, merely betrays ignorance and needs instruction. So-called specialists of this type are being eliminated by the spread of knowledge not only among the medical profession but also among patients. For the same reason it may be expected that the use of drugs or nostrums for diabetes will soon disappear and the express or tacit endorsement of the mineral spring superstition will cease.

Together with the satisfactory agreement on the purpose and benefit of scientific treatment, there exists a healthy state of doubt and disagreement concerning ways and means. Scarcely any two persons are treating diabetes alike in all details. Some lay emphasis upon protein, others upon carbohydrate, and others upon fat for attaining the optimum composition of the diet. A chemically balanced ration for avoiding acidosis is stressed by some, maintenance of the best ni-

trogen balance and general nutritive state by others, and strict regulation of total calories for avoiding hyperglycemia by others. The points at issue are all details which can be settled after a sufficient period of experience by the accumulation and presentation of unprejudiced facts, and it is highly gratifying that the debate is of the friendliest character and all the participants are recognized as striving for the advancement of scientific knowledge rather than for a partisan triumph. Valid objective evidence, including observations of sufficiently long duration, is thus the one requirement to be stressed throughout.

The views of the present writers have been derived originally from two sources, namely the animal experiments performed by one of us as set forth in this Journal and in former publications, and the experience with human patients in the Rockefeller Institute Hospital³ from 1914 to 1919. This published series comprised 76 cases; the minimum length of observation of any case in it was 16 months. The total deaths up to the time of publication were 33; these included every fatality up to that time (out of 100 cases actually treated); also 5 of the deaths were due to strictly non-diabetic causes, and a number of the others were due to various degrees of infidelity to treatment. The cases in general were severe. It is a conservative statement that no such prolonged control of symptoms had ever before been reported in any series of equal severity, and the subjective and objective improvement in health and appreciable prolongation of life sufficed to win acceptance for the new method as a therapeutic advance. On the other hand, some early mistakes were inevitable; also, owing to divided and antagonistic control, the clinical service failed to follow the lessons learned from the animal experimentation concerning caloric restriction, and all the severe cases treated with high calory diets showed plain downward progress. The course which was criticized in that monograph (p. 575) as a "record of blunders and mismanagement" stands further revealed by tracing the cases up to the present time, as shown in Table I.

TABLE I.

Fate of 76 Rockefeller Institute Patients, 1922.

22 Children (under 20 years of age) with various grades of diabetes

Dead	20
Living	2

31 adults (20 years or over) with severe diabetes

Dead	30
Living	1

23 adults with mild diabetes

Dead	6
Living	6
Not traced	11

There was never any scientific justification for the policy of reckless overfeeding above criticized. By it, the opportunity for an accurate trial of the possibilities of treatment was lost, but the actual record must be given in the interest of the mercilessly exact data above emphasized, irrespective whether it reflects upon individuals or possibly invalidates all claims made in behalf of this treatment. There will presumably be some critics who will hold either that the treatment itself is valueless, or that its hardships drive patients to break diet and that they succumb more quickly to the consequences of such violations after they have been weakened by the rigorous treatment. Such an argument, however, can have no scientific force until the objector shall take an equal series of cases of similar severity and undertake to keep them alive for an equally long time with any of the older methods which permitted active symptoms to continue. Until this highly improbable result is achieved, the conclusion of the monograph referred to stands intact, namely that "the method has accomplished more benefit than could be achieved by any former plan of treating diabetes, but that much better results than those obtained in this series of cases are possible in the future". The greatly superior results actually yielded by the method in the hands of competent and experienced workers, among whom Joslin is notable, afford further support to this conclusion.

Much wider credence will be granted to a contention that these and all other statistics prove that diabetes, particularly in its severe forms, is a hopelessly progressive disease; that it may be arrested a little longer by extreme care in treat-

ment than by a looser regime, but that the course is irresistibly downward and the end inevitably fatal. The greatest loss in connection with the above mentioned series lay in the inability to make the contemplated test of this current clinical belief. Attention may be called, however, to certain features of the record which were pointed out as significant in the writing of the monograph, and which are still so considered.

The 23 mild cases may be disregarded, for it is well known that such patients often live many years under any treatment or none, and most of the deaths recorded actually occurred from non-diabetic causes. There is fair reason for supposing that most of the patients not traced are alive, as they were symptom-free and well trained in taking care of themselves when last heard from.

Of the 31 severely diabetic patients above 20 years of age, it is observed that 30 are dead and only 1 living. The living case is No. 24, one of the severest of the series as judged by emaciation, weakness, difficulty of control, and permanently low tolerance. The known onset of diabetes was at 36 years, and the patient was received for treatment at the age of 44 years. With a height of 173 cm. and normal weight of 75 kg., he had been reduced by diabetes to 44.2 kg., and after a prolonged and severe regime of fasting and undernutrition his gradual improvement never reached the point of allowing him to weigh more than 45 kg. or to take a diet of more than 60 to 70 gm. protein, 10 to 15 gm. carbohydrate and approximately 1500 calories, but he has remained able to supervise his business with practically no interruption on account of health. The cause of the diabetes was apparently pancreatitis due to cholecystitis. Nothing was done to remove the original source of infection, but this has since remained quiescent and the diabetes has shown no progressive tendency. The case is not to be compared in severity with some of the younger and inherently more dangerous cases of the series, even when these were received at an earlier stage. Nevertheless it was a severe case which had been progressing markedly and continuously downward, which required rigorous measures for control, and which ceased to progress after symptoms were controlled by diet. It was mentioned several times in the monograph as illustrating the benefits of undernutrition. The inability to tolerate high diets without glycosuria was in fact a blessing

to several patients, for on the lower diets to which they were thus restricted they outlived a number of others who were admitted in a milder stage and who accordingly received excessive diets.

Of the 14 cases in the second decade of life, 1 has survived; and of the 8 cases in the first decade, 1 also has survived. The average total duration of diabetes in the living patients in the second decade at the time of the previous report⁴ was 41 months, and of those in the first decade was 16 months. Owing to the war and other causes, it was not possible to learn the exact time of death in a number of the cases, but a fair average will be reached by adding about one year to the above duration. The evidence for any great prolongation of life in 20 of the 22 cases in these two decades is therefore not very strong. An inquiry is necessary whether the two surviving cases differed from the others in type or in treatment. Patient No. 66 was a girl of 15 years, received for treatment March 6, 1916, 5 months after the supposed onset of diabetes. Patient No. 76 was a boy aged 4 years, received for treatment March 9, 1917, 2 or 3 weeks after the apparent onset of diabetes. In the monograph mentioned, attention was repeatedly called to the fact that these two patients, under the care of Dr. Fitz, received different treatment from the others; they escaped the excessive diets to which the others were subjected, their total calories were regulated so as to keep the blood sugar normal, and their clinical progress was contrasted with that of other cases which were similar in age and apparent severity. The latter, with their forced diets and hyperglycemia, not only died earlier but also showed obvious downward progress in shorter periods of observation. The girl, who broke diet by stealing fat (butter) for a considerable time, progressed downward into severe diabetes before the source of trouble was discovered and effectually removed, but has remained in an apparently stationary condition since that time. The boy has been continuously faithful to diet, and has passed safely through a long series of acute infections which have befallen him together with all the members of his family. Whether these have lowered his tolerance at all remains undetermined, but his diet still supports a satisfactory nutritive state, as shown by his published photograph⁵. It is evident that a longer series of cases of this character might cast doubts

upon the current belief in the inevitable and invariable progressiveness of typical cases of youthful diabetes. Such observations might thus afford valuable information not only concerning methods of treatment but also concerning the nature of diabetes.

As the second attempt to contribute to this question has now reached a stage fit for publication, the problem is encountered of presenting the clinical results in some clear and objective form as free as possible from prejudices of interpretation. Tables afford the only means of reasonable brevity, yet there is difficulty both in choosing and in classifying the cases. If the plan chosen meets with approval as just and comprehensive, we hope that it may be adopted by others for the sake of comparison. This plan is explained as follows.

1. Every diabetic specialist sees occasional patients only for the purpose of a single consultation, at the request of either themselves or their physicians. Some of them live at a great distance; others expect to remain under the care of their regular physicians, or to do as they please. Their sole purpose in coming is to obtain advice on the single occasion. The consultant does not take them under treatment or accept responsibility for their future, and seldom learns what becomes of them. The inclusion of such cases in a report of therapeutic results can be neither intelligent nor just, and it is only important that this class be not used as a convenient means of dodging responsibility for unsatisfactory results. The writers have employed this classification on the following basis:

(a) Of the total number of 643 diabetics seen, 138 came only for consultation without proposing to undertake treatment, and are therefore excluded as cases for which no responsibility was assumed.

(b) With an insignificant number of exceptions, these patients had mild diabetes, as is likely to be the case with those who request merely an incidental opinion. There is a reasonable expectation that all but a very few of them are alive, and the inclusion of this group would certainly make the general statistics appear much more favorable.

(c) Any deaths that occurred shortly after consultation, on account of complications or dangerous states then existing, have been included in the following tables.

2. The physician is called to see certain patients, or the patients are admitted to hospital, with dangerous complications such as coma or infection already present. As these conditions have not developed under the diabetic treatment, they are not a test of the treatment of diabetes as such but only a test of the treatment of these complications. These cases are therefore considered separately in Table II. Patients seen only in single consultations, or when already in extremis, are included. Those who recovered and undertook the regular treatment have been included in the subsequent tables.

3. All patients who came with the intention of undergoing treatment, and who did not die of the preexisting complications just mentioned, have been included in the statistical summary of Table III.

4. For the sake of information concerning degree of severity, fidelity to treatment, and character of results, the details of each case have been presented as fully as possible in Table IV. In addition, subsequent papers will give more complete records of patients who have died under treatment, and also of living patients showing representative methods and results in severe cases. This is done in the belief that the study of diabetes is at a stage where accurate data of this kind may again have genuine scientific value, as in the time of Külz and Frerichs.

TABLE II.

Complications existing when patients were first seen.

	1919		1920		1921		TOTAL	
	Living.	Dead.	Living.	Dead.	Living.	Dead.	Living.	Dead.
Gangrene	3	1	6	4	3	1	12	6
Pulmonary Tbc.	1	1	0	4	7	4	8	9
Coma	1	1	2	3	0	2	3	6
Neoplasm	0	1	0	0	0	0	0	1
Carbuncle	0	0	2	0	3	2	5	2
Total	5	4	10	11	13	9	28	24

REMARKS ON TABLE II.

Too long a digression concerning the treatment of diabetic complications would be inimical to the principal purpose of this paper, and the figures in Table II will mostly speak for themselves. The complications represented create the most dangerous situations in diabetes, and no apology is offered for the very high mortality.

The 18 cases of gangrene were mostly in an advanced stage when seen. The deaths comprise 2 in which amputation was stubbornly refused even when it obviously offered the only chance of saving life, and others in which sepsis and fever were present when the patients were first seen. When a diabetes (often originally mild) is fanned to intensity of glycosuria and acidosis by septic infection, while at the same time resistance to the spread of the infection is reduced by the diabetes, the combination is well known as excessively critical, and the great majority of such patients die with or without operation. On the other hand, the outlook for simple dry gangrene is much brighter than before. Of 15 cases of this type in this series, in 10 the necrosis was superficial and healed smoothly under diet. In the remaining 5 cases the gangrene involved bones and tendons of the feet at the time the patients were first seen. When the deep structures are thus involved, spontaneous healing is impossible and operation inevitable. The absence of systemic infection permitted preliminary diet treatment in all these cases; therefore acidosis was abolished and the plasma sugar brought below 0.2 per cent before operation, except in 2 cases, in which operation was hastened because of advancing gangrene and rise of blood sugar with low-grade intoxication. In no case of the entire dry gangrene series was there palpable pulsation of any vessels about the ankle. In 1 case amputation below the knee gave a good result. In the others, amputation above the knee was necessary because the vessels lower down proved to be almost occluded. All operations were performed under anesthesia with nitrous oxide and oxygen, without glycosuria, acidosis, or other accidents of any kind. In 1 case of very refractory diabetes coupled with extreme arteriosclerosis, healing was very slow and the patient left for his distant home before it was complete. There he overstepped his diet so as to bring back glycosuria, and a granulating sinus was still present at

the time of his death 9 months after operation. In the other 4 cases healing was both prompt and complete, and all are alive with no further trouble from gangrene. A few surgeons still fear to have patients undernourished before operation, but the above results show that such treatment gives far better results than operations performed in the presence of active diabetes. There is probably no difference of opinion among diabetic specialists concerning the fact that strict dietetic treatment offers the best chance for healing if the limb can still be saved and the best surgical success in cases requiring operation.

Diabetes with tuberculosis represents another combination in which each condition tends to make the other worse. When either disease is at all severe, the ultimate prognosis may be considered hopeless. Any extreme limitation of diet undoubtedly affects the tuberculosis adversely, but not so much so as a state of active diabetic symptoms. After trying stricter and laxer regimes, we have adopted the middle course of nourishing as liberally as possible without producing glycosuria or acidosis but without attempting to prevent hyperglycemia unless in exceptionally favorable cases. This gloomy ultimate prognosis does not mean that treatment is useless in this condition. The cases with cavity formation and fever, especially in youthful patients with severe diabetes, are the worst and generally run a rapid downward course, as the infection has its usual influence in breaking down the food tolerance and the diabetes lowers resistance to the infection. Nevertheless, even in these most hopeless cases, diet treatment sometimes accomplishes a striking gain both in comfort and length of life, as exemplified in a case previously reported⁶. In a middle class may be placed cases of more or less severe diabetes complicated with fibroid phthisis. Here the toxic absorption is less and the prognosis correspondingly better. The one living patient among those seen in 1919 was of this type. He was aged 30 years at that time, and may have had both diabetes and tuberculosis for the preceding two years according to the rather vague history. With symptoms of bronchitis, tubercle bacilli were numerous in the sputum in one examination, but both the bronchitis and the bacilli quickly disappeared under strict diet treatment. It proved feasible to build up a tolerance of 70 gm. protein, 25 gm. carbohydrate and

1600 calories, while keeping the blood sugar normal. Through unwise attempts at work and many departures from diet, tolerance has gradually been lost and finally bacilli have reappeared in the sputum. If we had planned better for supervision of the patient while at home, the favorable result could have been maintained much longer in such a case. The third group to be mentioned are the older patients with diabetes and tuberculosis in milder forms, and some of these permit the best results of all. Therefore, notwithstanding the bad general outlook, and the fact that no ultimate hope is entertained for any of the patients in Table II with this combination, diet treatment offers enough benefit that it should be carried out accurately in practically all such cases, even when stringent measures are necessary to stop the glycosuria. Whether there is a short terminal stage in which glycosuria and moderate acidosis should be permitted is a matter for judgment in the individual case. Our belief is that tuberculosis sanatoriums should not undertake to treat cases with diabetes unless prepared for accurate management of the diet. Such patients are unwelcome in a diabetic institution because of their special needs and the possible danger to other patients. A real want is therefore filled by the combined treatment offered by such a place as the Potter Clinic in Santa Barbara, California.

Diabetic acidosis remains an extremely dangerous complication when it has been allowed to develop to the stage of coma or pre-coma. The earlier stages are generally easy to check and have not been included in Table II. The cases there shown were in an advanced stage when seen, as is sufficiently indicated by the mortality. No patient has developed coma or serious acidosis under treatment, for when the under-nutrition regime is properly carried out there is no need for such accidents. For reasons of brevity, as mentioned, it is impossible to enter into a detailed analysis of methods or results. It is also not desired to enter into the prevailing discussion over the use or non-use of alkali. Our results in attempting to treat the extreme stages of diabetic acidosis have been bad, as shown by the fact that 6 patients died and only 3 survived. The majority of these patients received sodium bicarbonate in various ways and quantities, mostly by mouth. Joslin uses no alkali, and his results, which he has partly published and

doubtless will later publish more fully, are the best ever recorded, as judged by the fact that he has saved a greater number of patients having lower plasma bicarbonate figures than any other writer. The difference in methods between the different persons who use the newer diet methods is really slight, as it pertains to only a few cases. There is seldom any need for soda, and most competent judges will doubtless agree that the more moderate degrees of diabetic acidosis can be cleared up easily and smoothly by diet alone. It is a natural inquiry why we cling to the use of bicarbonate in the small number of desperate cases, if statistics carry any weight and if Joslin's results appear better than our own. Our excuses are three. First, we believe that the high mortality is due to the excessive severity of our cases. This cannot be proved by the plasma bicarbonate figures, which were higher than those of Joslin's cases and also higher than those in a number of the acidosis cases in the Rockefeller Institute series³ which recovered. This bicarbonate level was due to the considerable quantities of alkali which most of these patients had received before we saw them, and which according to Joslin's view might increase their danger. Second, the results in the cases treated without alkali were as fatal as those in the cases with alkali, and the three patients who recovered were among those who received alkali. Third, in 2 instances (one of the cases mentioned, and one seen in 1922) progress which seemed highly unfavorable under treatment without alkali was apparently turned to recovery by administration of sodium bicarbonate.

However this question may be decided, there can be no doubt of the great service rendered by Joslin toward correcting the prevalent abuse of alkali. Not only has bicarbonate been used to the exclusion of more rational measures for dangerous acidosis, but many physicians have prescribed it as a routine upon the first appearance of acetonuria or even at the first diagnosis of diabetes. Attention should be centered upon preventing the formation of acids rather than upon attempts to neutralize them. Therefore the milder grades of acetonuria are cleared up by stopping the loss of sugar in the urine and by properly balanced diets. For impending coma, the most important measure is the withdrawal of all food except the carbohydrate of citrus fruit juices, made into drinks for administering maximal quantities of fluid. Vigorous purga-

tion apparently helps. Additional fluid may be given intravenously or subcutaneously when needed in the form of saline solution. Alkali injections are sometimes dangerous and seldom if ever helpful, but we have observed no harm from reasonable doses of sodium bicarbonate by mouth or rectum during the emergency. All are agreed upon the principal features of this plan. If the mortality from coma can be reduced as low everywhere as in Joslin's clinic, the question of alkali will be seen to have small practical importance.

Two points, however, still deserve emphasis in regard to diabetic complications. One is the preeminent importance of prevention. Patients who are kept acetone-free do not go into coma, and the avoidance of coma is one of the main reasons for thorough treatment of diabetes in young patients. Patients whose diabetes is thoroughly controlled are no more subject to gangrene, carbuncle, cataract, retinitis and the like than non-diabetic persons of similar age and physical state, and the avoidance of these troubles is one of the main reasons why diabetes should always be carefully treated in the elderly, even when it appears to be merely a harmless glycosuria.

The other point to be mentioned is the apparent increase in the severity of diabetes. The treatment of acidosis consists in facilitating the elimination of poisonous material already present and in reducing the production of poisons by a regime which inhibits excessive fat metabolism and favors carbohydrate utilization. When the basic power of carbohydrate metabolism is too low, all treatment must fail. For this reason occasional patients who are seen before they are unconscious, and when their condition still seems to offer hope, go on into fatal coma irrespective of alkali or any other therapy. Also not the intensity of the temporary symptoms, but the tolerance which can subsequently be attained is the true measure of the severity of diabetes, and the possibilities of weight and strength are limited in proportion to this severity. For the purpose of testing the new treatment in the Rockefeller Institute Hospital, the attempt was made to select the severest possible cases of diabetes, and the belief was stated⁷ and has not been questioned that the average severity in this group was greater than in any which had been used for the trial of any previous treatment. Out of 21 coma patients, 14 were saved, mostly with but sometimes without the use of alkali. Also normal blood

sugars were generally possible within a fairly short time on what appear now as fairly liberal diets. The better success with coma, and the higher subsequent tolerance, both prove that few if any of the Rockefeller series of cases were as severe as a number of those in the present series. This degree of severity is occasionally due to the intrinsic character of the disorder or to delayed diagnosis, but on a wide scale appears to us as the result of more general understanding of methods for the temporary control of diabetes. When serious acidosis threatened, especially in a young patient, there was formerly urgent haste in sending him to the nearest specialist or to an institution such as the Rockefeller Institute; and as these dangers commonly arose early under the old plan of high diets, strict treatment could usually avert the crisis and often revealed a fairly high assimilative power. These possibilities became common knowledge, so that now not only most physicians but also many diabetic patients are aware of the means to use for warding off coma. Also, the most brilliant success appears to consist in building up a high diet as rapidly as possible and in thus transforming a critical state into one of apparent health. The "starvation treatment" has unfortunately been widely misunderstood in this temporary sense, notwithstanding many warnings that the subsequent diet is more important as well as more difficult than the initial fast. Accordingly, patients are freed from symptoms by such measures, relapse on improper diets, and repeat these cycles long past the time at which they would formerly have died in coma. The hydropic degeneration of islands meanwhile brings the absolute food tolerance constantly lower, until a stage of severity is reached in which coma is nearly hopeless, life is possible only in a state of extreme emaciation if at all, and the scarcity of islands of Langerhans at autopsy gives a clear reason for the condition. These circumstances may differ in different countries and places, but in this region the explanation of the severity of many cases seems to be found in such partial treatment.

TABLE III.

Mortality of cases classified by years in which first seen.

1919

Decade	Total Cases	FAITHFUL TO TREATMENT					ABANDONED TREATMENT					Total Mortality %
		Cases	Living	Dead	Cause of death	Mortality %	Cases	Living	Dead	Cause of death	Mortality %	
1	2	1	1	0	2 inanition 1 influenza 1 nephritis 1 inanition	0.0	1	1	0	1 coma 1 coma	0.0	100.0 50.0 0.0 33.3 25.0 0.0
2	6	5	3	2		40.0	1	0	1		100.0	
3	4	2	2	0		0.0	2	1	1		50.0	
4	6	6	3	3		50.0	0	0	0		0.0	
5	11	5	5	0	2 coma 1 cirrhosis of liver	0.0	6	4	2	2 coma 1 cirrhosis of liver	33.3	29.4 22.2
6	10	6	6	0		0.0	4	3	1		25.0	
7	6	3	3	0		0.0	3	3	0		0.0	
	45	28	23	5		17.9	17	12	5		29.4	

1920

1	6	2	2	0	1 inanition	0.0	4	1	3	3 coma	75.0	26.6 26.6 40.0 0.0
2	13	7	7	0		0.0	6	2	4	4 coma	66.6	
3	16	8	8	0		0.0	8	2	6	6 coma	75.0	
4	20	9	8	1		11.1	11	7	4	3 coma, 1 neuro-syphilis	36.3	
5	29	14	14	0	1 uncontrollable severity	0.0	15	11	4	3 coma, 1 nephritis	26.6	26.6
6	32	17	16	1		5.8	15	11	4	2 coma, 1 nephritis 1 psychosis	26.6	
7	14	9	8	1	1 apoplexy 1 heart failure	11.1	5	3	2	2 coma	40.0	42.2 23.4
8	3	3	2	1		33.3	0	0	0		0.0	
	133	69	65	4		5.8	64	37	27		42.2	

1921

1	22	14	14	0	1 inanition 1 pneumonia	0.0	8	5	3	3 coma	75.0	20.0 31.2 0.0 14.2
2	30	22	22	0		0.0	8	3	5	1 pneumonia, 4 coma	62.5	
3	20	15	15	0		0.0	5	4	1	1 coma	20.0	
4	48	32	30	2		6.2	16	11	5	5 coma	31.2	
5	69	50	49	1	1 inanition	2.0	19	19	0	1 coma, 1 inanition 1 gangrene	0.0	0.0 0.0
6	71	50	49	1	1 inanition	2.0	21	18	3		14.2	
7	33	26	26	0		0.0	7	7	0		0.0	
8	9	6	6	0		0.0	3	3	0		0.0	
	302	215	211	4		1.8	87	70	17		19.5	6.9

Total
for 3
years

480 312 299 13

4.2 168 119 49

29.7 12.9

REMARKS ON TABLE III.

The cases in this table are divided according to the years in which they were first treated at this Institute, irrespective of the previous duration of the diabetes. * In one class have been placed those who still report in person or by mail for advice, and who are reasonably faithful to diet. In another class are placed all who have abandoned the treatment, by discarding all restrictions, or refusing to follow advice, or changing to some other physician, or removal to too great a distance, or in any other way. The mortality figures cover all deaths among these patients up to Jan. 1, 1922; i.e., the deaths recorded for the respective years are not limited to those occurring in those years.

Thus, there were 45 patients treated in 1919, of whom 28 have remained faithfully under treatment up to Jan. 1, 1922, and 17 have broken or changed treatment. Among the 28 faithful, the deaths up to Jan. 1, 1922, have been 5, or 17.9 per cent. Among the 17 unfaithful, the deaths have been 5, or 29.4 per cent.

In 1920 there were 133 patients received for treatment, of whom 69 have remained faithful to Jan. 1, 1922, and 64 have abandoned or changed treatment. Among the 69 faithful, the deaths up to Jan. 1, 1922, have been 4, or 5.8 per cent. Among the 64 unfaithful, the deaths have been 27, or 42.2 per cent.

The patients seen for the first time in 1921 numbered 302. Of these, 215 continued faithful to treatment to Jan. 1, 1922, and 87 abandoned or changed treatment. Among the 215 faithful, the deaths up to Jan., 1922, have been 4, or 1.8 per cent. Among the 87 unfaithful, the deaths have been 17, or 19.5 per cent.

Increased mortality is naturally to be expected with passage of more time, from both diabetic and non-diabetic causes. Thus, reckoned up to Jan. 1, 1922, the total mortality among the patients treated in 1919 has been 22.2 per cent, that among the patients treated first in 1920 has been 23.4 per cent, and that among the patients received in 1921 has been 6.9 per cent. The total mortality for the 3 years amounts to 62 among 480 patients, or 12.9 per cent.

These figures serve to show the results regarding preserva-

* A few patients first seen in 1918 (cf. table IV.) are here included in the 1919 group for convenience.

tion of life among patients undertaking regular treatment, whether this was continued faithfully or not. For statistical interest, the total may be completed by adding the deaths shown in Table II, which occurred from initial complications, so that they did not serve for a test of the regular treatment. Thus, the deaths from initial complications in 1919 were 4, and those among treated patients were 10, making a total of 14 among 49 patients, or 28.6 per cent. The deaths from initial complications in 1920 were 11, and those among treated patients were 31, making a total of 42 among 144 patients, or 29.2 per cent. The deaths from initial complications in 1921 were 9, and those among treated patients were 21, making a total of 30 among 311 patients, or 9.6 per cent. The entire mortality thus was 86 among 505 patients, or 17.0 per cent.

Observations concerning mortality.—The difference in death-rate between unfaithful patients and those faithful to treatment is sufficiently marked to encourage strictness and fidelity, especially as there can be no doubt in the minds of those knowing these individuals that the latter class have also had easier and more comfortable lives than the former. Additional notice may be taken, however, of the fact that the mortality among the unfaithful patients is not strikingly high, especially in relation to the severity of the cases as indicated by their age and food tolerance. When the patients merely turned to other physicians, the treatment of these latter may receive credit, but this was true in only a minority of instances. The great majority of those who broke off treatment gave up attempts at diet, or tried faith cures or quack remedies, or violated the diets of the physicians to whom they subsequently applied. In the great majority of cases, therefore, glycosuria was brought back, and the statistics apply to this condition. They serve, for one thing, to refute an impression which has gained some acceptance, that the weakening effect of an undernutrition treatment hastens the death of such patients as subsequently break diet. This impression may sometimes be created by cases which have gone on for years, until such a severe stage has been reached that life can be saved only by drastic measures. Such patients may be kept alive for a certain time by such measures, and then, if they tire of the hardships and eat recklessly, may die rather quickly, but the actual fault lies not in the later strictness which kept them alive but

in the earlier laxness which brought them to such a state of severity. It was previously pointed out^s that the overwhelming majority of such patients die not from inanition but from coma. There can be no valid doubt that they are safer from acidosis after the acetone has once been thoroughly cleared up and the body weight reduced, and the above statistics give a further illustration of this fact. In addition, few patients totally forget the discipline of a properly conducted institution, the instruction in food values received there, and the lessons learned from their observations of other patients. Some confirmed violators of diet are thus reformed. Even those with the least intelligence or self-control generally make at least occasional efforts to stop their glycosuria or restrain it within moderate bounds, and the results are evident in the longer duration of life. Their downward progress, however, manifests itself not only by increasing symptoms but also by the rise of mortality with each year that goes by.

Observations concerning causes of death. — Of the 49 deaths among patients unfaithful to treatment, 37 were due to coma. Two deaths were due to other diabetic causes, viz. inanition in one case and gangrene in another. Another patient went insane and died a few weeks later, the trouble being probably independent of her diabetes. There were 4 deaths due to definitely non-diabetic causes, viz. nephritis (2 cases), cirrhosis of the liver (1 case), and cerebrospinal syphilis (1 case). Among the patients faithful to treatment, inanition was responsible for the greater number of deaths, viz. 7. The plain meaning of this term is that the diabetes was so severe that death resulted after a longer or shorter period from starvation, due to inability to acquire tolerance for any living diet. In 1 case of this sort coma was finally permitted as the alternative, the condition being entirely hopeless notwithstanding the patient's fidelity. The death from influenza pneumonia in 1 case may have been independent of diabetes, as the infection was then epidemic, but responsibility will nevertheless be accepted under the head of diabetes, as this may have heightened the susceptibility to the infection or the attendant weakness may have induced the fatal result. Three of the fatalities were definitely independent of diabetes, viz. nephritis, apoplexy, and heart disease, 1 case each.

By a reckoning on this basis, the death-rate from diabetes

in this series could be somewhat reduced, if desired. It is more important, however, to call attention to the lack of diabetic complications among the cases under treatment. Except for the 1 case of hopeless severity, coma was absent because acidosis was not permitted. Tuberculosis has not appeared in any patients other than those (Table II) in whom it was present at entrance. The patients faithful to treatment have also enjoyed complete immunity to gangrene, carbuncle and other complications. As active diabetes is far more dangerous than undernutrition in creating susceptibility to all sorts of infections and injuries, the same may be expected to hold true for tuberculosis. The strongest possible emphasis should therefore be placed upon strict dietetic control for the prevention of tuberculosis as well as all other diabetic complications.

Observations concerning fidelity to treatment.—Some former opinions of the unreliability of diabetics are untrue, for the majority of them will follow diet conscientiously when convinced of the benefit and instructed in regard to accurate and appetizing preparation of food. They have not always been treated fairly in statistics, which have been planned to show as low as a death rate as possible under institutional care and have not taken proper account of those who were discharged as hopeless to die at home, where they might break diet either from ignorance, despair, or intolerable privations. It is essential that any treatment shall be not only theoretically advantageous but also suitable for practical application. The test of any dietary regime is two-fold; first, the benefit to patients who actually follow it, and second, the proportion of patients who will consent to follow it. Thorough control imposes hardships proportioned to the severity of the diabetes, but on the other hand it inspire confidence if real control is achieved and if the benefit is sufficiently evident to convince the patient. The atmosphere of fidelity and hope in a diabetic institution depends upon its results, and in turn is the greatest aid to further results. The menus must be so prepared as to avoid any intolerable suffering from hunger. With rational conduct thus made possible, patients of average intelligence and self-control will be governed more by the actual experiences of themselves and the other patients whom they meet than by anything that any physician can tell them. The fact that such a large proportion of them will continue faithful

even under extreme privations affords good evidence of benefit.

As figures can always be juggled, attention may be given to the possibility that the easier and more favorable cases are counted in the faithful class, while the severe and discouraging character of other cases results in violations of diet and also in a higher mortality among the unfaithful group. Such a suspicion may be answered and a basis of judgment afforded by two facts. One is the proportion of faithful and unfaithful patients. If cases are unduly relegated to the unfaithful list, the figures for mortality under treatment may be improved but those for fidelity will suffer, and the total results will still show the actual saving of life accomplished. In the present instance, we believe that the proportion of faithful patients will bear comparison with any similarly frank statement of experiences with the use of any looser regime. The second fact to be noticed is found in the detailed case records of Table IV, which show that the question of faithfulness or unfaithfulness is decided more by the character of the patient than by the character of the diabetes or the diet, and that no unfaithful patient has been called upon to face greater hardships than have been borne by a number of those who have persevered in fidelity.

REMARKS ON TABLE IV.

Number of Cases.

This table is intended to give the records of the entire series of 505 cases in as full detail as feasible, in order to aid judgment of the severity and the results of treatment.

Sex.

The male patients numbered 258 and the female 247, thus conforming to the view that sex is immaterial in the etiology of diabetes.

Race.

The racial distribution is significant. The Jewish patients numbered 254, against 251 for the total of all other races. Of the latter, 216 could be classified only as Americans. The patients of pure immigrant stock comprised 17 Germans, 4 of

Spanish or Spanish-American origin, 3 Italians, 1 Norwegian, and 1 Dane. The preponderant representation of Jews, who constitute a comparatively small element in the total population, harmonizes with the belief in their special liability to diabetes.

Occupation.

The list of occupations serves chiefly as an index of the social status. Manual laborers are a minority. The series comprises charity patients as well as paying patients, but the former are chosen as strictly as possible on the basis of character. The latter are a wholly unselected group of richer and poorer, more and less intelligent types. Though the rich are sometimes exceptionally hard to manage, and even education gives no guarantee of co-operation in treatment, nevertheless as a general rule dietotherapy is more successfully applied in the upper social strata than in the lower. A clinic which deals chiefly with the poorest and most ignorant classes must be regarded as laboring under a disadvantage and allowances made accordingly for its results. On the other hand, it is questionable if the average character of these patients is any different from that of the majority of persons who consult diabetic specialists or patronize resorts or institutions for this disease. Most physicians doubtless feel that their results are impaired by difficulties of one kind or another, but it is not fair to place the blame upon the patients or the environment unless some proof can be offered that these are worse than the ones encountered by others.

Age and Date of Admission.

The age at admission and date of admission refer to the time at which treatment was begun. The great majority of the patients received institutional care and instruction for periods ranging from 1 week to several months, and afterward were supervised by means of office calls, while they followed their diet at home generally unaided but in a few instances with a nurse or dietitian in charge.

Previous Treatment.

The next column briefly summarizes the treatment of the patients prior to admission. At one extreme are those who

underwent no restrictions of diet whatever, either because of their own carelessness or because of delayed diagnosis. There are unfortunate instances in which diabetes has run a typical and severe course in a child or young adult for a year or more with no diagnosis until an extreme stage of emaciation and acidosis had been reached. There is still need for greater care on the part of the general profession in making urinalyses of all their patients, controlled by blood analyses if necessary. At the other extreme are patients whose diabetes was diagnosed on the first suspicious symptom and who received thorough treatment from the outset. The great majority, however, fall in the class of lax or partial treatment, the inadequate control being attributable to the genuine difficulties of a severe case, or to carelessness regarding a mild case perhaps diagnosed merely as "glycosuria", or to disobedience on the part of the patient.

In one respect all dietary restriction is beneficial, for it undoubtedly relieves symptoms, retards downward progress, and lengthens life. The great mass of cases must be treated by general practitioners, and the average longevity of diabetics may be expected to increase more in proportion to the improvement of methods used by the general profession than in connection with particular refinements employed by specialists. In another respect inadequate treatment is injurious and unjust. The mild glycosuria of the elderly patient may thus be allowed to go on continuously or intermittently for years, until severe diabetes, gangrene, infection, blindness, or some other preventable calamity results. The inherently dangerous diabetes of a child or young adult may thus be palliated in its mild early stage, when glycosuria is easily checked by fasting and a condition of health can be more or less perfectly imitated by means of over-liberal diets. Regardless of warnings that this course is neither safe nor merciful in the long run, many practitioners and parents cling to the idea that a short and comfortable life is better for the youthful patient than a longer existence of emaciation and invalidism. They do not, however, carry out this belief logically by feeding the patient so as to keep up his weight and strength as long as possible and then allowing an easy death in coma. On the contrary, they follow this course till either acidosis or emaciation becomes too threatening, and then bring

the patient in to have his life prolonged as far as possible by the extreme measures which alone can avail at that stage. The complaint was made above that this partial treatment is responsible for many of the excessively severe conditions now encountered, and the resulting emaciation and invalidism are blamed upon the undernutrition treatment when the fault properly lies with the regime which reduced the tolerance to such a minimum.

Duration of Diabetes.

The duration of diabetes, as shown in the next column, is dated from the first discovery of glycosuria or the first unmistakable symptoms. The duration prior to admission is necessarily an uncertain quantity, since there is probably a long latent period in the average case before the diabetes becomes active, and some further time generally elapses before the active diabetes is recognized. The only positive fact, therefore, is that the diabetes was present for at least the length of time mentioned. The figures for the duration after admission and the total duration are reckoned up to Jan. 1, 1922, or up to death for any patients who died before that date. Averages and other computations will be more useful after the treatment has been carried on for a greater number of years. Certain observations may be mentioned in comparison with a statement by Joslin⁹, that in the Massachusetts General Hospital up to 1898, 67 per cent of all patients who died of diabetes succumbed during the first year of the disease, and of his own fatal cases up to 1915, 17 per cent were fatal during the first year. He states in his preface that acutely fatal diabetes is now disappearing. In the present series (covering both the treated cases shown in Tables III and IV and those with complications shown in Table II) the deaths within the first year of diabetes in the first 3 decades of life were limited to 9 patients who flagrantly broke diet (Nos. 168, 381, 410, 489 and 1043 in the first decade, No. 61 in the second decade, and Nos. 221, 456 and 474 in the third decade.) All of these discarded every dietary restriction and ate everything without limit. Not a single patient under the age of 30 died within the first year of diabetes if diet was faithfully observed or was broken only within some bounds of moderation. The only death within the first year of diabetes in the fourth decade

of life was that of patient No. 801, who had an unusual condition requiring repeated abdominal operations, and who was personally faithful, but was later taken away by his surgeon and allowed to develop glycosuria, and who then died of infection. It cannot be claimed that stricter treatment could have offered a much better result. In the fifth decade of life there was also one atypical case (No. 125) which appeared like an ordinary early mild diabetes, but which ran a resistless course of edema and cachexia; the extreme arteriosclerosis may have been a factor. Altogether, therefore, the deaths within the first year of diabetes among the 505 patients comprised in Tables II to IV amounted to 11, or 2.2 per cent.

Length of life with diabetes also affords some criterion of treatment. Figures for patients past middle age are almost impossible of interpretation, because of the variability of cases and the long duration which can rightfully be expected of most of them. It therefore means little that some of the older patients of this series have lived through 10 to 30 years of diabetes. The figures for the third, second and first decades of life possess an ascending order of importance, because the more severe and rapidly progressive character of cases at these ages permits the accumulation of more decisive data within a shorter period of observation. The cases of this series beginning within the first decade of life and having a longer duration than 3 years may be shown in tabular form as follows.

TABLE IV A.

7 cases in first decade with duration above 3 years.

Case No.	Age at Onset. Years	Treatment before Admission	Fidelity	Total duration Years	Condition Jan. 1, 1922
75	2	Partial	Fair	4	Fair
97	8½	Partial	Fair	5⅔	Good
123	7	Partial	Good	4	Good
229	4½	Partial	Fair	5	Fair
553	9	Good	Diet	5½	Dead
			abandoned		
708	8½	Partial	Good	3	Good
881	6½	Partial	Good	3	Good

In this table, partial treatment before admission means that the patients were kept free from glycosuria except on com-

paratively few occasions when either the diet was broken or a gradually increasing hyperglycemia finally manifested itself in the urine. Practically all of them came to this Institute because of the slight downward progress experienced under such a program. The parents of patient No. 553 were discouraged with diets because the child, though nearly normal in appearance, had reached the point where further reduction of diet and weight was necessary instead of the increase which they desired, and they came seeking a cure of the diabetes. When they found that nothing but strict weighing of food and limitation of the child's weight and strength could be offered, they soon gave up their efforts, and death within 6 months was the result. It is confidently believed that practically any of these cases could be thus terminated, and their long duration is not due to exceptional mildness but to careful treatment. As our own period of observation is comparatively short, it is a pleasure to recognize that this result is due chiefly to the care of other physicians, most of them general practitioners. The fact that, out of a total of 37 cases* in the first decade of life, 7 patients have lived from 3 to 5 years and 6 of them are apparently able to live a considerable time longer, stands in contrast to the very small proportion of such patients who survived more than 3 years under former methods of treatment. It may be excusable to reiterate the conviction that the children are also more comfortable and happy than under any treatment which permits glycosuria. Though the above results now appear exceptionally good, we have no hesitation in expressing the further belief that application of thorough treatment from the earliest stage can make survival beyond three years the rule rather than the exception, even in cases in the first decade of life.

Results in the second and third decades of life should in general be better than in the first decade. A similar tabulation, however, of the cases of this series would show actually a smaller proportion of long survivals. The difference is not due to any greater severity or progressiveness of the cases in the second and third decades, as judged by our experience in bringing them under control, but rather to the fact that

* In Table III were listed 30 patients who were in the first decade at admission, and 7 of those who were in the second decade at admission had the onset of their diabetes in the first decade.

the previous treatment afforded fewer instances of the necessary combination for such survival, viz. physicians to prescribe the proper diets and patients willing to follow them. Our independent experience, as mentioned, is still too short for the purpose, though the living and faithful patients are numerous enough to furnish material for such a study hereafter. One example of what can be done is furnished by case No. 783. This girl developed diabetes early in 1913, at the age of 13 years. After some preliminary dieting, her physicians communicated with the Rockefeller Institute, and were advised to use treatment to control both glycosuria and hyperglycemia. The patient and her parents co-operated to the utmost, so that glycosuria was kept absent though some degree of hyperglycemia was present most of the time. Both tolerance and weight were very slowly lost, and at admission in 1921 the case had reached a severe stage, though a tolerance of 55 gm. protein, 15 gm. carbohydrate and 1000 calories was still attainable and sufficiently strict oversight promises a considerable further prolongation of life. The case appears entirely typical, the longer duration as compared with other cases seems attributable to the treatment, and it is believed that a similar longevity is possible for the majority of patients at this age with sufficiently strict treatment from the outset.

Height and Weight.

The columns showing the height and weight of patients permit judgment of their state of nutrition. It must be remembered that the weight figures are sometimes considerably confused by dryness of the tissues at admission and by edema after treatment.

In the following tables (IV B and IV C) a compilation is made with reference to obesity, showing all children (first 2 decades) who were 5 pounds or more above average normal weight, and all adults who were 20 pounds or more above average weight before the onset of their diabetes. The standard normal weights in these tables and in Table IV are taken from Joslin¹⁰.

TABLE IV B.

Cases in 1st and 2nd decades 5 lbs. or more above standard weight before diabetes.

FIRST DECADE		SECOND DECADE	
Case No.	No. lbs. over standard weight	Case No.	No. lbs. over standard weight
489	6	61	33
518	9	134	14
843	5	135	13
1021	9	175	26
		184	7
4 cases		274	21
		339	5
		443	16
		510	14
		543	12
		581	22
		708	5
		764	58
		780	35
		826	5
		1046	31
		16 cases	

These observations confirm those of Joslin in showing that obesity is one of the most prominent contributing factors in the production of diabetes in adults, but is less frequent in children.

The degree of emaciation gives some indication of the severity of the case at the time of admission, and the most reliable one of all is the further reduction of weight which is necessary to abolish glycosuria and obtain the desired control of the blood sugar. These observations are collected in Tables IV D and IV E, the former showing all children who at admission were 5 pounds or more below standard normal weight, and the latter all adults who at admission were 20 pounds or more below the standard. Some instances of marked loss of weight in obese patients are thus omitted, but in general the weight in relation to a normal standard is a far truer index of severity than the mere number of pounds lost by a fat person. Also, this plan omits some cases in which the weight was nearly normal at admission, but in which a radical reduction was necessary for therapeutic control. It is believed that extreme stubbornness of glycosuria, or of hyperglycemia especially in youthful cases, is a very important indication of severity. This therapeutic reduction, however, can scarcely

TABLE IV. C.

Adults 20 pounds or more above normal weight before diabetes.

Case No.	Pounds above standard weight	Case No.	Pounds above standard weight	Case No.	Pounds above standard weight	Case No.	Pounds above standard weight
7	44	329	93	596	62	811	31
16	26	335	38	597	65	812	58
34	37	345	38	601	38	815	35
36	117	346	54	602	44	818	46
42	46	350	33	610	30	827	65
47	23	352	51	612	30	830	37
49	33	356	29	613	25	833	38
59	26	359	24	617	28	835	48
61	33	360	34	620	67	837	51
66	21	361	90	621	57	840	30
77	29	368	46	624	38	841	93
90	43	370	49	629	53	844	23
94	91	374	36	631	41	845	66
98	44	375	151	635	76	847	46
100	43	393	68	638	128	848	34
126	61	396	52	639	25	849	34
131	38	402	26	641	34	852	45
136	71	404	28	642	134	857	34
144	48	422	25	646	67	869	45
151	38	431	77	649	74	873	115
158	62	437	79	654	27	874	62
161	25	438	77	658	74	884	56
171	58	441	36	667	41	892	48
173	26	448	20	670	57	894	56
180	26	452	69	673	23	902	132
208	24	453	29	677	67	903	40
216	33	454	63	678	67	905	38
218	116	455	68	686	35	917	37
221	20	457	27	687	22	932	51
225	22	461	38	688	96	947	62
235	23	468	25	694	25	951	54
236	30	477	51	698	43	953	38
239	25	478	45	700	30	955	45
241	78	480	61	711	29	959	31
243	74	486	27	712	26	962	42
254	34	491	30	718	28	963	74
258	25	492	73	719	94	964	48
262	23	495	66	723	47	965	24
265	38	503	53	745	28	980	29
280	30	504	38	754	55	984	32
288	35	505	63	758	35	987	33
290	26	509	39	761	54	1018	88
294	56	511	73	767	42	1029	49
295	46	515	43	770	41	1030	77
301	47	516	48	773	69	1032	37
304	27	520	69	776	53	1038	43
305	29	524	108	785	61	1039	36
307	31	525	42	787	50	1040	57
312	28	536	54	788	99	1047	24
318	28	542	37	789	25	1050	29
321	38	553	39	805	58	1060	51
324	35	588	22	807	82	1062	53

serve as a basis of comparison, because of the widely different standards used by different physicians for judging whether the condition is under satisfactory control. Some of the weights shown in these tables may serve, however, in conjunction with the ages, as a basis for approximate comparison of these cases with those of other writers.

TABLE IV D.

Cases in 1st and 2nd decades 5 lbs. or more under standard weight on admission. Total of 79 cases.

FIRST DECADE			SECOND DECADE		
Case No.	Pounds under standard weight on admission	Change in body weight since admission. Pounds	Case No.	Pounds under standard weight on admission	Change in body weight since admission. Pounds
44	8	— 7	1	15	—20
75	7	— 4	23	56	—12
123	8	+13	175	18	—17
331	10	— 2	184	10	— 3
363	8	— 2	187	21	— 1
381	6	— 1	205	23	— 3
410	8	— 2	336	19	—15
539	14	+ 7	337	37	— 4
541	16	+12	339	12	+ 1
574	11	— 4	340	12	— 3
603	10	— 2	384	11	—18
616	6	— 1	443	12	+12
747	6	— 3	465	26	+ 7
768	10	— 2	474	19	— 1
806	12	— 3	514	42	— 1
834	11	— 4	534	11	+30
843	10	— 2	540	22	—11
881	12	— 3	553	18	— 1
1070	30	— 2	578	10	+ 6
<hr/> 19 cases			587	16	—19
			659	6	— 1
			709	11	— 1
			759	19	— 7
			780	5	— 2
			786	22	— 3
			826	30	— 5
			911	50	—11
			970	18	— 6
			1009	30	— 4
			1016	35	—17
			1020	14	— 4
			1052	13	— 3
			1055	13	— 4
			1069	46	— 2
			<hr/> 34 cases		

TABLE IV E.

Adults 20 pounds or more under standard weight on admission.

Case No.	Age.	Pounds below standard weight on admission.	Pounds reduced after admission.	Case No.	Age.	Pounds below standard weight on admission.	Pounds reduced after admission.	Case No.	Age.	Pounds below standard weight on admission.	Pounds reduced after admission.
5	27	21	7	317	27	28	3	718	51	30	8
6	62	40	20	320	37	25	8	724	70	60	16
24	27	50	12	328	26	31	30	725	45	68	19
25	43	51	12	343	59	27	27	731	29	42	15
31	35	51	6	347	50	32	2	734	55	45	1
41	33	54	20	355	58	37	11	739	30	21	3
49	64	20	7	356	33	22	2	743	47	45	17
56	36	22	5	371	31	37	20	746	51	32	1
60	30	23	33	382	24	20	8	752	55	61	5
69	59	27	12	391	47	23	3	753	35	47	11
70	28	29	11	402	48	24	9	766	37	49	16
76	27	30	16	409	32	32	0	767	70	39	14
77	48	21	7	413	25	31	4	771	55	28	1
84	53	24	7	423	33	30	11	774	36	45	2
85	31	52	12	432	59	54	10	790	39	52	4
100	63	24	20	436	47	40	23	793	56	85	9
125	52	66	22	439	31	75	4	795	27	72	14
137	45	36	3	447	35	24	11	801	35	56	6
145	43	46	10	448	36	49	4	813	32	54	5
149	55	41	5	457	56	21	10	816	46	24	1
150	35	22	1	466	40	38	10	818	45	30	9
156	22	37	12	471	33	25	2	820	38	26	7
160	58	55	9	475	62	29	4	823	25	57	9
162	50	36	2	476	21	44	2	824	49	23	16
168	37	54	6	487	35	23	10	828	44	49	1
173	36	21	39	499	51	83	2	833	36	47	18
174	42	47	11	509	51	33	8	837	41	20	8
177	25	29	20	511	61	40	22	839	43	46	15
180	70	25	10	515	60	21	18	840	63	28	3
200	53	21	3	526	48	31	8	844	64	35	7
208	43	21	5	531	51	35	33	846	29	25	1
211	60	35	8	532	24	23	15	849	60	28	13
212	63	22	5	535	44	40	12	856	29	40	2
214	26	41	3	542	46	40	4	863	24	36	9
219	41	53	2	548	30	62	20	867	25	22	9
225	55	49	18	573	33	25	20	874	47	35	10
228	64	32	23	591	44	35	16	885	50	35	1
232	40	25	8	611	61	31	5	915	30	32	2
235	45	25	14	612	59	33	6	926	50	41	10
242	69	27	4	618	34	38	6	927	64	26	4
246	24	32	5	620	50	20	14	932	40	41	23
248	42	36	18	629	37	37	32	947	47	28	2
251	56	29	2	642	32	29	5	949	55	37	3
265	49	29	25	647	55	43	10	975	32	25	4
283	29	38		653	36	39	8	1003	40	26	10
286	55	78	5	654	57	40	13	1012	55	21	1
291	49	46	13	668	60	42	4	1033	56	23	12
304	45	57	16	676	29	33	16	1044	47	42	9
312	56	42	3	683	56	41	1	1048	41	70	11
314	43	40	9	687	61	41	14	1049	49	51	18
315	32	40	4	693	65	30	3	1058	37	31	1
								1063	76	73	5
								1073	26	46	10
								1074	43	56	1

Complications Present at Admission.

The table of complications in Table IV is mostly self-explanatory. Table II showed only the cases with complications endangering life at the time of admission. In addition to these, all patients with complications of lesser degree are included in Table IV. The milder grades of acidosis have been ignored altogether. Only the cases with coma present or impending were represented in Table II. Intermediate degrees mentioned as "acidosis" in Table IV were characterized by marked ferric chloride reactions, appreciable quantitative outputs of acetone and ammonia, and sometimes moderate reduction of the CO_2 capacity of the plasma. Formerly, therefore, they would generally have been classed as examples of severe acidosis, but they are now cleared up as a matter of incidental routine. Being so largely determined by the character of the previous diet, they deserve no special emphasis and have only slight value as a measure of the intrinsic severity of the cases.

With the exceptions mentioned in Table II, the infectious complications have either healed spontaneously or become amenable to operative cure. Arterial hypertension is a separate disorder and has usually yielded to appropriate sodium chloride restriction. Nephritis carries its own prognosis, sometimes more serious than that of the diabetes. Neuritic pains have ceased almost without exception after a longer or shorter period of thorough dietary control. The 4 cases with hyperthyroidism have not been characterized by any special severity or difficulty of control, and the 3 cases with cirrhosis of the liver have shown no tendency to cessation of glycosuria other than that naturally associated with their fall in weight. Diet treatment offers no hope for an existing cataract, except normal healing of the wound when the removal is performed. Diabetic retinitis has been arrested in every case in the writers' experience by means of a diet which has controlled the blood sugar. Every gangrene of superficial tissues, not involving bones or tendons or accompanied by general sepsis at the time when first seen, has healed smoothly and recurrences have remained absent whenever the diet has been faithfully observed.

The writers have previously placed emphasis upon the fact that not a single diabetic complication has ever occurred in any of these cases under thorough dietetic control, and this

immunity to some of the chief causes of suffering and death in diabetes is alone worth all the privations of the diet. Recently two instances of mild and transitory neuritis have occurred in patients who were permitted to have continuous moderate hyperglycemia (without glycosuria) on account of their age. Such a record must be credited partly to good luck. Retinitis and various infections and accidents sometimes happen to non-diabetics. Gangrene is entirely possible without diabetes, when arteriosclerosis is so far advanced that no pulsating vessel can be discovered anywhere about the ankle, as in nearly all the gangrene cases of this series. Also, as the elderly are most subject to these complications, and as strictly normal blood sugar values are seldom demanded of them, the possibility of some genuine diabetic abnormalities must be admitted. The fact remains that fairly efficient control of the sugar improves the function or resistance of tissues throughout the body to such an extent that the long-familiar complications of diabetes are to all intents and purposes abolished. There is reason to hope that arteriosclerosis, so far as it is secondary to diabetes, may be prevented when even the mildest cases of glycosuria are treated with proper care from the outset.

Initial Treatment.

The plan followed is that outlined in a former publication.¹¹ Immediately after admission, instead of continuous fasting, the patient is placed upon a very low diet consisting chiefly of protein. When there is any marked acidosis, carbohydrate is also given. Fat is omitted except in some mild cases, when low calories in this form are allowed. These minimal diets, especially by their protein content, maintain a better level of strength and comfort than absolute fasting, while the therapeutic result generally is about the same. The addition of a little carbohydrate with exclusion of fat serves to clear up acidosis, so that no danger is ever encountered from this cause except when the patient is in or near coma when received (Table II). The proper culinary employment of materials for giving bulk, such as bran, agar, celluloflour, thrice-boiled vegetables, mineral oil, thin soup, coffee, etc., tends to regulate the bowels and also makes this regime so satisfying that many patients fail to realize that they are practically fasting.

The figures shown in this column represent grams of protein

or carbohydrate, without added calories of fat unless the total calories are specified. This point is emphasized because the extreme degrees of undernutrition represented in some instances may prove startling. For example, it is meant literally that patient No. 219, whose weight originally was 125 pounds and who was admitted almost in coma and emaciated to 93 pounds, was kept on 20 grams of protein daily for 6 weeks, except for interspersed days of complete fasting. The final weight was 91 pounds, because of water retention without visible edema, in contrast to the original dried state. Other examples of extreme privation will be found in Table IV, but will not be detailed here as they will later be published more fully. They have physiological interest as examples of the degree of undernutrition which can still be endured by persons who are emaciated at the beginning. Therapeutically, they may be defended on the principle that it is the physician's duty to promote both life and comfort as far as possible. It will be observed that these extreme examples are rare, and that the initial treatment has always been made as short and easy as the character of the case permitted, so that the great majority of patients have not complained of hardships during this time. If a quick and easy death had been the aim in the extreme case mentioned, it could have been assured within a few hours by allowing the patient to go on into coma; but there was no way of knowing in advance that this case would be so severe and would not respond as readily as the majority.

Complaint was made above of the excessive degree of severity to which diabetic patients are sometimes brought by partial treatment, which fails to halt their decline of tolerance but yet extends their lives far beyond the point at which they would formerly have died in coma. It was suggested that blame for this result belongs to the lax treatment which produced it rather than to the rigorous measures which alone can prolong life at this stage. If other physicians encounter cases in which not mere hyperglycemia but actual glycosuria requires a program of this character for its suppression, they will appreciate what is meant by the word severity as applied to cases in this series. The question then is whether patients who are proved to belong in this class should be subjected to further privations or should be fed liberally with a view to a shorter but more comfortable life. We have never dared to

impose a diet which would knowingly shorten life, because a few of the most difficult cases finally show a capacity for improvement and longevity beyond anticipation. Also, comparative observations of patients dying under extreme inanition and those dying with active diabetic symptoms produced by lax diets or by violations of diet have convinced us that suffering is distinctly less under the former program. We have, therefore never consented to the continuance of glycosuria except in still rarer cases of still greater severity, namely those in which glycosuria cannot be stopped at all.

Final Diet.

The figures in this column of Table IV indicate protein, carbohydrate and total calories in the order mentioned. It is to be understood that the "initial treatment" is continued long enough to gain the desired result, namely a normal level of blood sugar in young patients and at least cessation of glycosuria and acidosis and a reasonable reduction of hyperglycemia in older patients. A gradual increase of diet is then begun, controlled by blood sugar analyses, and continued until the level of the "final diet" is attained, generally within the period of a few weeks or a month or two, and before the patient leaves the Institute. When the treatment is broken off at an incomplete stage, the "final diet" is merely the highest one attained and is not one upon which the patient is expected to live. When the treatment is carried to completion, the "final diet" is the one upon which the patient is allowed to go home, with the expectation of increases or decreases according to the later blood sugar tests. These subsequent changes cannot be given in detail, but it is to be understood that the ultimate diet attained is one that suffices to support the "final" weight given in the body-weight column, unless the remarks in the "Result" column specify differently. In the great majority of cases there is no important change from the "final diet" as given. It is furthermore to be understood that these diets, with scarcely any exceptions, are interrupted by days of partial fasting taken regularly once every week, when the total ration is reduced generally to one-half or one-fourth of the usual amount. In this manner the average diet is reduced a trifle below the figures stated. The value of these fast-days cannot be definitely proved, but we have the very decided impression

that results are better with this plan than when the same amount of food per week is distributed equally through the seven days. Von Noorden's conception of "metabolic Sundays" may furnish a figurative explanation.

It is desired to emphasize two points in connection with these diets. First, they represent undernutrition, in the sense that the patient's body weight is kept permanently below the original level and generally below the level at the time of his admission. In cases of obesity, this may mean merely a reduction of the quantity of surplus fat, leaving the absolute weight at, or only slightly below (in some mild cases actually a little above) the normal standard for that height. With increasing degrees of emaciation at entrance, and with increasing severity of diabetes, more advanced grades of undernutrition are required for the control of symptoms. As above mentioned, we have not hesitated to carry this regime to any point needed for this purpose, in the belief that both life and comfort are thus conserved. The main point is that the old idea of the desirability of building up the body weight in diabetes is absolutely rejected, and the hope of controlling symptoms and preventing downward progress is based upon the principle of holding the patient's weight merely at the best level which is permitted by his diabetes. It is unfortunate when severe diabetes requires a severe reduction of weight and strength for the attainment of any lasting control, but two facts may be pointed out. First, thorough treatment of mild or early cases is possible without such harsh measures, and this is the proper stage for such treatment not only for the sake of the best immediate results but also for the avoidance of progress downward into the severe stage. Second, it is hardly fair for opponents of undernutrition to argue as though severely diabetic patients had not always been thin and weak, or as though they possessed any magic formula for keeping them plump and strong, or as though the old-time plan of high-calory diets for the sake of temporary nutrition and satiety had not proved so disastrous that a reversal of it promptly won the support both of diabetic patients and of the general medical profession.

The second point may be more surprising, namely that these diets are actually higher than the opponents of undernutrition have ever been able to use while keeping glycosuria absent in cases of similar type. It is only necessary to have agree-

ment that diabetics are better off when they can be maintained in nutritive equilibrium on some diet which keeps symptoms absent. Granting this one premise, examples may be taken from cases not uncommonly seen in consultation, when a specialist may say; "This patient has a tolerance for only 30 grams of protein and 500 calories per day, without carbohydrate. If he is kept on this diet, he will starve to death, and if the diet is raised, glycosuria and acidosis will soon bring on coma". As a matter of fact, many diabetics have wasted away on such a regime, the diet being reduced when coma threatened, then raised in the attempt to restore strength, and this alternation continued to death from either inanition or coma. As a contrast, it will be noticed that in even the severest cases of this series completion of treatment has almost always resulted in tolerance for a diet of 30 calories per kilogram of weight. In cases like the example cited, rigid initial undernutrition accomplishes three things besides abolishing glycosuria and hyperglycemia. First, it lowers the body weight, so that the same absolute ration comes to represent a larger ration per kilogram. Second, it markedly lowers the caloric requirement as calculated for the surface area by the old Meeh or the new height-weight formula¹², and this reduction of metabolism allows the maintenance of equilibrium on a lower absolute ration. Third, it raises the tolerance, so that a higher absolute diet can be taken while preserving the freedom from acidosis and hyperglycemia. Very few cases therefore are incapable of reaching an equilibrium, and this combination of events was summarized in the previously published statement⁵ that "almost always the curve of rising tolerance intersects the curve of falling weight at a level on which life can be maintained". As downward progress in assimilation is also thus checked to the greatest possible extent, it follows that the nutritive equilibrium thus established can be maintained either indefinitely or for a longer time than under any other plan, and this fact supports the conclusion that both life and comfort are longest preserved in this way.

Degree of Fidelity.

This topic was discussed under Table III. All writers have complained of the transgressions of diet by diabetics, no matter how liberal the diets allowed. There may be some force

in the argument that theoretically ideal diets should not be enforced too rigidly, that the patient should be considered as well as the disease, and that better results on the whole will be obtained by milder restrictions because a higher proportion of patients will observe them. It is worth pointing out on the other hand that consideration of the patient cannot well be carried to the point of neglect of the disease. The measures used have been as mild as seemed capable of controlling the disease, but never mild enough knowingly to permit progress of the disease. Continuous absence of glycosuria and acidosis has been required wherever at all possible, but most of the elderly patients have been subjected only to such moderate reduction of hyperglycemia as seemed necessary for safety against downward progress or diabetic complications. The additional demand of continuously normal blood sugar has been imposed upon practically all young patients, because this plan involves greater difficulty only at the outset and in the long run seems as easy as the insistence upon mere aglycosuria, while the assimilative power and thereby the nutritive equilibrium are believed to be preserved much longer, as already stated. Reliance has been placed upon two principles; first, that the methods which actually afford the best control of the diabetes are the ones which win the greatest confidence of the patients and thereby the best co-operation; second, that hunger and other discomforts are more wisely relieved by pleasant environment, highly skilled preparation of menus, and other suitable devices than by injurious laxity of diet. These results have been achieved to the extent that the great majority of patients go through their period of greatest privation without the slightest grumbling or dejection. The trouble comes chiefly after discharge, from ignorance, lack of self control, the contrary advice of some physicians, the allurements of faith cures and other delusions, and all the temptations which beset a person who knows that his disease is incurable by present scientific methods and that his future is only one of limitations and privations. Under these circumstances it is not surprising that so many patients break diet either slightly or flagrantly, and gratification may be felt that the majority of patients have proved strictly or reasonably faithful to the procedure outlined. If it be admitted that any rules of accurate diet are beneficial in diabetes, it is certain that some proportion of pa-

tients will break these rules. Due weight should be given to the fact that most of the patients recorded as having abandoned diet were faithful for considerable periods. If any equally frank record of results by other writers shows a higher standard of loyalty after a similar lapse of time, it must be admitted that their treatment is superior from the standpoint of securing the fidelity of patients.

Results.

The results as regards mortality were discussed under tables II and III. As regards general health and the things that make life worth living, it can be said that the results in the milder cases of later life are eminently cheerful. The privations of diet are not serious, the patients are able to work and enjoy themselves practically the same as if they had no abnormality, and through simple precautions they have the prospect of completing their full span of years in comfort, or even perhaps living longer than if these precautions had not been forced upon them. There can be no doubt that the development of the dietetic treatment of diabetes has accomplished enormous benefit by means of these results in the great multitude of mild cases, and by saving these patients from diabetic complications and from transition into the severe stage.

The life of the severely diabetic patient is one of hardship and limitation. All attempts to ignore his diabetes and feed him up to a state imitating the normal in weight and strength are fatal, and prolongation of life is possible only by recognition of the existence of the disease and acceptance of a degree of invalidism proportioned to its severity. No attempt need be made to conceal the tragedies thus involved, and it would be wrong to suppose that the results of the present treatment are at all satisfactory. We believe it to represent an advance over former methods with respect to both the longevity and the comfort of patients, and also to be the most thorough possible means of controlling the disorder by the passive method of sparing function, until something in the nature of an active cure shall be discovered. Aside from accidents, the patients who are willing to accept the necessary privations may still die from one of two causes, namely from starvation or from progress of the diabetes, and a few remarks may be devoted to each of these possibilities.

Starvation is inevitable when the patient in his initial treatment proves unable to acquire tolerance for any diet sufficient to support life. Unless coma is allowed to supervene, he must die from emaciation whether glycosuria is permitted or not. The actual minimum diet for indefinite maintenance of life is not known, but seems to be considerably less than 30 calories per kilogram for extremely thin and weak patients spending most of their time in bed. Deaths from inanition have been witnessed after periods of a year or more, as the result of diets which were barely below the minimum requirement. The majority of inanition deaths, however, have been due not to lack of the necessary minimal tolerance at the time when the patient was first seen, but to a gradual decline of tolerance with progress of the diabetes. The paradoxical conclusion holds, therefore, that the best safeguard against inanition consists in sufficiently thorough undernutrition at the outset, so as to attain the highest diet and at the same time prevent downward progress. The feasibility of this latter aim is the most important point to discuss. The few cases of this series in which the present diet seems to involve any danger of starvation will be described more fully in a later paper.

Progressiveness of Diabetes.

As previously mentioned³, "spontaneous downward progress" has been the excuse for every kind of mismanagement, blunder and failure of diabetic treatment. The worse the treatment employed by any physician, the more glibly will he declare that some cases of diabetes inevitably run downhill to death, and the larger proportion of such cases will there be in his practice. This belief originated in the observations of the earliest textbook writers, who published detailed case records of the transition from the early stage into the severe late stage, according to what they regarded as the natural evolution of a hopeless disease. Some such cases were those occurring after middle life, and with improvements in diet treatment it became recognized that cases of this sort were mostly progressive only on improper diets, and that with suitable diets their progressiveness could generally be halted. The conception of inherent progressiveness was then limited to all typical cases in youth and a few in later life. Naunyn clearly enunciated the principle of sparing a weakened function by rest, so as to prevent its further deterioration from over-strain,

but he also believed in inherent progressiveness of the more severe cases and gave an example¹³. This was a case in a girl of 26 years, who became free from glycosuria on carbohydrate restriction and remained so for three months. The meat ration was increased to 600 gm. daily. Glycosuria reappeared and could not be checked, and the dietary restrictions had to be relaxed in order to avoid coma. He concluded, "Hier macht sich wie gesagt die Progressivität der Krankheit geltend, obgleich die gestörte Funktion bis zum äussersten geschont wurde". Few will now doubt that the "Altmeister" of diabetes was here mistaken, that the disturbed function was by no means spared to the utmost, and that at least a very appreciable prolongation of life could have been accomplished by sparing it more efficiently.

Under the head of duration of diabetes above, reference was made to Joslin's observations of the practical disappearance of acutely fatal diabetes and the diminishing number of deaths within the first year of diabetes. It is illuminating to make comparison with figures given by Naunyn¹⁴. He quotes statistics of Griesinger and Pfeiffer published in 1875, for 152 diabetics of all ages. Of these, 2 died within $\frac{1}{4}$ year from the time of onset, 15 within $\frac{1}{2}$ year, 30 within 1 year, 47 within 2 years, 31 within 3 years, and 12 within 4 years, while the remaining 15 patients lived from 5 to 14 years. Naunyn considered these figures too unfavorable, and therefore gave the results of 141 cases at all ages from his own private practice. In his series, 42 patients died in the first year of their diabetes, 35 in the second year, 23 in the third year, 14 in the fourth year, 5 in the fifth year, and the remaining 22 at longer intervals. These figures deserve the attention of persons who question whether the treatment of diabetes has improved, for few writers in this country today would care to confess to such results. They are quoted, however, to show how Naunyn, who recognized the rôle of overtaxed function in causing downward progress, still believed that these cases ran a natural course within these comparatively short periods of time.

As the cases in late life can generally be held stationary or improved, it is also coming to be understood that most cases in young adults can by careful treatment be kept in check for at least a considerable number of years. The doctrine of irresistible progressiveness finds its strongest support in the

juvenile cases. Here reference may be made to the figures quoted by Naunyn from Külz, concerning 46 cases in children under 14 years of age. Of these, 16 died within 3 months, 14 within 6 months, 5 within 1 year, 6 within 2 years, 4 within 3 years, and 1 lived 4 years. Naunyn regarded these results as indicating the rapid progressiveness of diabetes at these ages, but today there can scarcely be a question that inadequate treatment was the chief reason for such early deaths.

The fact was pointed out elsewhere¹⁵ that no pathologic basis has ever been found for this supposed spontaneous progressiveness of diabetes, and this has been one of the scientific mysteries of the subject. The lesions that might be progressive, such as fibrosis, round cell infiltration, hyalin degeneration of islands, etc., are found chiefly in the cases of later life, which are clinically least progressive. Some evidence was found in favor of the view that diabetes, especially of the youthful severe type, is commonly the result of an acute pancreatitis instead of a chronic or progressive lesion. On the other hand one process is known which parallels the clinical course in its progressiveness and involves progressive destruction of islands of Langerhans. This is the so-called hydropic degeneration, which is proved to be not a cause of diabetes but the result of diets which overtax the weakened island function. Accordingly, a definite pathologic basis exists for the downward progress from functional overstrain, but none has been demonstrated for the supposed spontaneous progress in typical cases.

If an answer to this question is to be found, it must be along the line attempted by Naunyn, namely that the damaged function must be spared to the utmost. Cognizance must furthermore be taken of the fact that the susceptibility to functional overstrain varies enormously in different types of cases. It is an elementary fact that the injury from improper diets is typically different in youthful cases and in elderly cases, irrespective whether this difference is phrased in terms of hydropic degeneration or of clinical progress. Owing to this greater resisting power in most cases past middle life, more liberal diets and some degree of hyperglycemia are generally permissible, and the long and variable course of such cases unfits them for decisive tests. The youngest patients, on the other hand, are known to be extremely susceptible to func-

tional over-strain, because of the very rapid downward progress resulting from excessive diets. The best clinical evidence, therefore, must consist in observations of the progress of such cases when the weakened function is spared as thoroughly as possible.

As a test of over-taxed function, hyperglycemia is considered preferable to glycosuria, for the following reasons. (a) This distinction is now generally accepted by physiologists in judging the effects of epinephrin, piqure, and similar experimental procedures, and it is altogether logical thus to exclude the mere accidental differences which can result from the wide variations in renal action. (b) Partially depancreatized dogs, fed so as to maintain continuous hyperglycemia without glycosuria, show downward progress which is fully similar in rapidity and in results to that observed in youthful human patients. To objections concerning the validity of this comparison with experimental animals, it may be replied; first, that every detail of clinical diabetes can be matched precisely in such animals, and the burden of proof therefore rests upon those who question the similarity of the disorder; second, that pains were taken by very long trials to ascertain that these animals were free from spontaneously progressive tendencies; third, that while some occult cause of progressiveness has commonly been assumed in human patients, to which animals with simple removal of portions of the pancreas are not subject, it would be very strange to reverse this argument by assuming a cause of progressiveness in the animals which is not present in patients. (c) So far as known, youthful patients with continuous hyperglycemia have invariably progressed downward. Some exceptional cases differ from the others in the length of their course, but if anyone has observed a young diabetic who has shown no decline of assimilation after several years of abnormally high blood sugar, the experience will be of interest for publication because of its uniqueness, but can only prove that a rare youthful patient may have a resisting power similar to that of the usual elderly patient. If there is any hope of preventing downward progress in typical youthful cases of diabetes, it can be found only in those whose assimilative function is spared to the extent of maintaining a constantly normal blood sugar.

Besides excesses in carbohydrate or total calories, the ore

other demonstrated cause of hyperglycemia and assimilative injury is infection. This term is meant in the bona fide clinical sense, and not to provide a loophole of escape by conjuring up mysterious undemonstrable foci. The question is whether, if these two causes of functional damage are avoided in cases of the typically severe and progressive type, the familiar decline of assimilation can be prevented. Both time and extent of experience are important for a decision. Two or three cases apparently held in check for a year or two cannot be decisive, because exceptional variations are not thus excluded. If one or several cases can be observed, in which the assimilation progressively declines notwithstanding continuous freedom from both hyperglycemia and infection, the fact will be highly important if positively demonstrated, but yet will leave room for similar criticism on the ground of possible exceptional factors. If a sufficient number of cases are studied under sufficiently thorough control, the time limits need not be prohibitively long, for changes of assimilation in the great majority of the severest cases are ordinarily very plain in the course of a year, and maintenance of undiminished assimilation in such a group for a year or more would be a highly instructive achievement. If the practical difficulties prevent perfect results, but if it is shown in general that with more and more efficient sparing of function the maintenance of tolerance and life is extended constantly farther toward indefinite prolongation, as a variable approaches a limit, the existence of a purely spontaneous factor in the causation of progressiveness will become improbable.

The observations in this series have created the impression that if diabetic patients could be shut up in cages and fed strictly according to theoretical indications, downward progress would be as little evident in typical human cases as in experimental dogs. They have strengthened the conclusion previously drawn³, that if any spontaneously progressive lesion exists at all, it is no more than a minor factor in the downward progress generally observed. "The traditionally rapid course of diabetes in infants and children indicates not an inevitably acute process in them, but rather a high degree of susceptibility to breakdown of their islands and their assimilation by over-strain."

Formerly this conclusion may have seemed too improbable

to deserve much attention. Now it may perhaps receive notice in the form of general dissent and opposition. The belief in the natural progressiveness of some types of diabetes has been so universal and unquestioned that it cannot be shaken quickly or easily, even though it has not a single accurate clinical or pathological observation for its support. The antagonism of clinicians will be aroused by the imputation that their own treatment has been the thing that has sent their patients downhill, and the best friends of the undernutrition treatment will consider that too much is claimed for it by a suggestion that it can prevent downward progress in the great mass of diabetic cases of the severest type. Here it is only necessary to draw a sufficiently sharp line between scientific and practical facts. The practical situation is that diabetic patients can seldom be held strictly to an ideal standard. Williams¹⁶ has published his results under a treatment which aims at maintenance of normal blood sugar, but he would scarcely claim that this ideal has been constantly achieved. Many mistakes and deceptions are committed by patients at home; even those under study in this Institute for this special purpose have had elevations of their blood sugar at times; and it is thus obvious how commonly the assimilation of ambulant diabetics is overtaxed to the extent of hyperglycemia. There is even the possibility that better practical results may be gained by those who impose a less arduous regime which commands better fidelity by not discouraging the patients; it only devolves upon those who use the laxer methods to prove this practical superiority. Furthermore, though hyperglycemia is our most delicate indicator of overtaxed function, it may (like glycosuria formerly) prove to be not delicate enough to give warning of all functional over-stain. Still again, if every detectable functional overload is avoided, the general wear and tear of life may exhaust a damaged organ prematurely, just as a patient with serious heart disease may meet a premature death even if both infection and exertion are avoided. Finally, in the severest cases the effects of the prolonged extreme undernutrition must be considered, and it is not certain that constitutional deterioration can be avoided or life maintained on such a basis.

Practical results, therefore, must speak for themselves, and it is not intended to stretch the claims for this method be-

yond the limitations shown by the actual figures. In addition to the immediate therapeutic purpose, it has been deemed a useful scientific endeavor to apply the principle of functional rest as thoroughly as possible in diabetic cases, with a view to accurate observations of the resulting progress. The purpose of their presentation to a limited number of scientific readers, instead of publication in a purely clinical journal, is to arouse a minimum of practical dispute and stress the scientific side of the question. It is true that if some individuals continue to find marked progressiveness in their diabetic cases while others can show longer life and little progressiveness, the suspicion may be aroused that somebody besides providence is at fault. Theoretically, if the downward progress in diabetes can be explained on the simple basis of functional deterioration in a damaged organ through functional overload, the clinical and pathological aspects of the subject will be illuminated and harmonized. Practically, though the difficulties of controlling diabetic cases may be as great as before, it will be highly important for the physician to know definitely the reason for progressiveness and the possibility of checking it. For these reasons it is still believed that this question of progressiveness is the most important one in diabetes, and no regret will be felt for having raised it, whatever the final decision.

The Work of Petré

The restriction of carbohydrate and protein and liberal use of fat was emphasized by all the writers of the past generation, and the recent exaggeration of this principle by Petré in Sweden deserves notice. This author's work has aroused interest in Europe but is little known in America. His latest publication outlines his results in a chosen group of cases, but a more complete monograph is promised for the near future. He began the use of his high fat diet especially in cases of serious acidosis, in the belief that the acidosis could be controlled by sufficient restriction of protein while the nutrition could be safely maintained by the fat. Encouraged by his favorable results, he extended this treatment to all severe cases of diabetes in his practice. His first table gives a synopsis of 17 cases in which the urinary nitrogen was kept below 4 gm. daily for periods of 20 days or longer. The nitrogen

of the diet was from 3.2 to 6.1 gm. daily, the carbohydrate 26.2 to 108.6 (mostly about 50) gm., and the fat from 113.6 to 320 gm. daily. The writer shows that he thus, with diets composed chiefly of fat, has approximately equalled the nitrogen minima established by the well known workers on this subject with diets chiefly of carbohydrate. Petré's initial diet for diabetics contains no meat, eggs, cheese, bread or milk, but is made up of green vegetables with butter, fat bacon, cream, etc. He also intersperses fast-days, one or two at a time, but considers longer fasting undesirable. This rigid program of fat and vegetables is continued uninterruptedly for periods of 10 to 50 or 60, or in one case 82 days. With improvement the restrictions are slightly relaxed, a few eggs being added, for example, but the entire idea is a continuously minimal protein metabolism, based on the belief that protein is the particularly harmful food in diabetes.

Petrén next gives, partly in tables and partly in text, the results of this treatment as applied to a large diabetic service from the year 1914 to the middle of 1920. For illustration he picks out the severest cases, judged by the fact that the blood sugar at entrance was 0.24 per cent or higher, and which did not end fatally in the hospital. He considers a blood sugar concentration above 0.3 per cent to represent an exceptionally dangerous diabetes. Some of the patients had D:N quotients of 3 or over (though these apparently were not determined on actual carbohydrate-free diets). Petré's shows that in 79 cases of the severe group the blood sugar was reduced under treatment, in 3 it rose, and in the remaining 3 it remained practically unchanged. In a similar large majority of the cases glycosuria was stopped, and acidosis either abolished or much reduced. The latter result may be attributed to the raising of the carbohydrate tolerance, so that some patients could assimilate 90 gm. per day or more. There was a decline of tolerance in only 6 of the cases, and in 7 of them the tolerance was practically unchanged. At the same time the liberal fat ration maintained nutrition so well that a large majority of the patients gained very appreciably in weight and strength.

In the same period (1914-1920) there were 41 deaths on Petré's diabetic service, though only 26 of them are attributed strictly to diabetes; 16 of these 26 occurred within 3 days after

admission, and 6 more within a week after admission, so only 4 diabetic deaths are counted for the remaining several weeks or months in hospital. Petréⁿ once tried the experiment of giving 150 gm. of meat on one day, and one of the fatalities is attributed to this cause.

Subsequent tracing of the above mentioned group of severely diabetic patients who did not die in hospital showed the following. Of the 44 treated from 1914 to 1917, 3 could not be traced, 6 were living in 1920, 6 were dead of other causes than diabetes, and 32 were dead presumably from diabetes. Of the 21 patients treated in the second period, 1917-1920, 9 had died of diabetes and 2 of other causes, while 10 were alive. The youngest living patient from the first period was aged 37 years, the 25 younger ones in this series having all died; from the second period there were living patients aged 15, 16 and 17 years. The time of death was also detailed; in 13 cases it occurred within 2 weeks to 6 months after discharge from hospital, in the others at longer intervals up to 3 to 5½ years.

Petréⁿ's work is highly commendable for its enthusiasm and the endeavor to present the facts fully and frankly. He interprets his results conservatively, recognizing that the diabetes is not fundamentally changed by a mere apparent gain of tolerance. Full agreement with him can be expressed on a number of points; for example, his strong support of the principle of sparing a weakened function, his use of a stringent program interspersed with fast-days for this purpose, his striving for a low blood sugar, and even his observation that the stopping of glycosuria may reduce acidosis notwithstanding a high fat diet. On the other hand, certain points seem open to criticism as follows.

First, though Petréⁿ may be justified in calling his illustrative cases severe in the sense formerly used by writers, they are obviously not severe in the sense in which the word is now used in America. Not only is his idea of an initial blood sugar concentration of 0.24 per cent as representing a severe case and 0.3 per cent as representing an extremely severe case entirely inadmissible, but also the fact that his patients could become free from glycosuria while taking 50 gm. of carbohydrate and sufficient fat to maintain or increase their weight is enough to classify them as mild in this country. Confirma-

tion may be found in the fact that 2 of them were obese and none seriously emaciated, the possibility of increasing the weight by as much as 10 kilograms without an immediately fatal result was still present, and the ages in most of the successful cases were significantly high. The evidence of mildness is completed by the fact that so many of the patients were able to live for considerable periods at home, evidently without weighing their diet or taking the other precautions which are indispensable in severe cases. The opinion may therefore be expressed that the severely diabetic patients were the 41 who died in hospital, and that the remaining milder cases were cleared up more slowly and less thoroughly than could have been done by the average American practitioner.

Second, however the results in such a group of cases may compare with those of the Naunyn method, neither the immediate nor the remote results can be called good in this country. The total mortality cannot be judged until information of the total number of cases treated is available, but the deaths among the chosen group who survived their hospital period were too numerous and occurred too soon after discharge. Among the group of 65 patients, from 1914 to 1920, whose record after leaving hospital was above quoted, only 16 were alive in 1920 and 49 were dead. These figures, of course, are incomparably inferior to those of Joslin, which cover a longer period of time. Petréⁿ complained that the Rockefeller Institute monograph did not give an adequate idea of the results obtained there, but he will find in Table IX on page 554 the record of 33 deaths among 76 patients. The period covered, from 1914 to 1919, was one year shorter than Petréⁿ's, but this difference was counterbalanced by the fact that the choice was made so as to represent at least 16 months of observation in every published case, some of Petréⁿ's observations being much shorter than this and his proportion of living patients being much higher among this group. The main difference is believed to consist in the far greater average severity of the Rockefeller Institute cases. The differences in the survival of children and young persons are also significant. Two pleas may be made in extenuation of the mortality among the Rockefeller Institute patients; first, it was due so largely to excessive fat diets; second, all members of the

diabetic staff entered military service and the subsequent treatment was not properly supervised.

Third, Petrén shows that the highest and earliest mortality among his cases occurred in those having the highest hyperglycemia and acidosis at admission. This statement proves the inability of his method to control the more severe cases. The degree of control achieved in the entire group may be declared unsatisfactory; the majority were discharged with hyperglycemia present and some also with glycosuria and acidosis. No statement is made of the symptoms following discharge, but it is evident that many among the cases called successful suffered an early return of both glycosuria and acidosis. There is no indication that the patients were properly trained to avoid these conditions.

Fourth, anyone doubting the fatal influence of excessive fat upon both diabetes and acidosis should refer to Petrén's results, obtained chiefly in patients possessing appreciable carbohydrate tolerance. The record of 22 patients dying within a week after admission, and 7 of the treated series dying within 2 months after discharge, speaks for itself. If the death of a patient 6 days after the feeding of 150 gm. of meat is attributed to the meat, the condition was very bad before the meat was fed. Petrén states that he has never been able to observe a harmful effect from fat, and assumes that the fasting and undernutrition employed at the Rockefeller Institute rendered the patients susceptible to such injury. If he will take young patients with genuinely severe diabetes, acidosis and emaciation, of the type who have formerly died early in his experience, he should have no trouble in convincing himself that they can be kept symptom-free by fasting and undernutrition and by no other means, and that the harmfulness of excessive fat becomes quickly evident in suitable tests. In milder cases it results in slower fatalities, as shown in Petrén's series.

Fifth, Petrén's views brings him into hopeless theoretical difficulties. The notion that protein, either as such or in the particular form of meat, is specially injurious in diabetes comes down through the literature from early times, but has never had any sound or rational basis of support. Petrén is even driven to question the rôle of fat in the production of acidosis and to argue for protein as the chief source of this

danger. Such theories, having no scientific foundation, would have to be supported by very positive clinical evidence, and this is obviously not afforded by Petré's results. Also, the attempt to spare a weakened function by rest has not been well accomplished by his method, which runs counter to the hypothesis of a deficiency of the total metabolic capacity in diabetes. He can scarcely deny that most or all of his milder cases have shown downward progress, while his high fat rations have not succeeded in building up weight or strength or even preserving life in a single case of genuinely great severity and progressiveness.

The work of Newburgh and Marsh.

Though the so-called "starvation treatment" was widely accepted when first announced, it has always had opposition, both intelligent and also from persons who have never read the original publications fully or carefully or given the plan an accurate trial. The word "starvation" has aroused some unjust prejudices, but in addition the actual limitations of the method are highly unfortunate. Patients with the severest diabetes must often be kept in a weak and emaciated state of invalidism, with nothing more hopeful promised for their future. It is inevitable that both they and their physicians should be inclined to rebel against such a starved life when it is due to direct limitation of food, forgetting that severe diabetes has always involved emaciation, that diabetic polyphagia is far more tormenting than the slight hunger experienced on well prepared diets, and that the results of treatment, however poor, are still preferable to active diabetic symptoms from every angle of longevity and comfort. Also, there is an evident ground for debate as to what balance of food materials will permit the highest level of nutrition and the best general results. It is thus natural that the pendulum should swing back toward high fat rations, and a strong wave in this direction has been started in this country by the publications of Newburgh and Marsh¹⁷ favoring a large preponderance of fat in the diabetic diet.

Their theoretical ground was the following. "It has been the general custom to make up the diet largely of protein, because of the undoubted desirability of omitting carbohydrate, and because of the almost universal fear of precipitating a

dangerous acidosis by allowing more than a minimum of fat. This leaves the physician the choice of one of two procedures. On the one hand, he may keep the patient sugar-free, but in so doing, because of the low energy intake, he renders him unfit for the ordinary activities of life. On the other hand, if he aims to avoid this for his patient, he must expect him to continue to suffer from the effects of hyperglycemia. We have dared to ignore the belief concerning the danger of fat in the diet of diabetics, and have investigated in the clinic the effect of a diet whose energy comes largely from fat, to which is added sufficient protein to maintain nitrogen equilibrium and the minimal carbohydrate necessitated in making up a diet that a human being can eat over a long period of time." They conformed their diets to Hindhede's estimate of 0.66 gm. of protein per kilogram of body weight, and their table shows reductions of the urinary nitrogen as low as 2.9, 2.4, or 1.2 gm. daily in consequence of the initial treatment. This treatment consisted in placing the patient at admission on a ration of approximately 900 to 1000 calories, of which the fat was 90 gm., the protein 10 gm. and the carbohydrate 14 gm. After one or two weeks of freedom from glycosuria, gradual increase of the diet was begun, so that a typical diet at discharge consisted of 1800 to 2500 calories, furnished by 30 to 40 gm. protein, 25 to 30 gm. carbohydrate, and the remainder fat. Their first paper described short observations in a series of 73 unselected diabetic cases thus treated with good results, particularly as respects avoidance of coma and clearing of acidosis. Their second paper extends these observations and shows that a normal level of blood sugar is often achieved by their method. In cases with nephritis, and in others classified only as not responding satisfactorily to treatment, the hyperglycemia was somewhat more refractory, though glycosuria and acidosis were controlled.

A broad basis of agreement with Newburgh and Marsh is established by their acceptance of a normal blood sugar as the goal of endeavor, and by their employment of initial undernutrition in severe cases, as expressed in the diets of 1000 calories or less. Their ultimate diets also are comparatively low, their examples of 1600 to 2500 total calories being decidedly different from the high rations given either by the classical German authorities or by Petré. This may be taken

as the reason why their results were so much better than those of either the Naunyn or the Petré methods. Three points of disagreement or criticism may, however, be taken up as follows.

1. The attack of Newburgh and Marsh seems to be directed against high protein diets, and their only clinical experiments consist in comparisons between their diets and others containing as much as 150 to 200 gm. of protein. The need of protein restriction has long been established, and low protein high fat diets were used routinely by Naunyn and his contemporaries for clearing up glycosuria without precipitating coma. The use of oil days, or of days when only a trifle of green vegetables was given with as much fat as possible, was also a tried method in their hands. In the Rockefeller Institute experience, the use of oil days and alcohol days was recorded, but all such attempts to maintain high nutrition were discarded after trial because they were found to defeat the real purpose of undernutrition. Also, some patients in that series were placed on carbohydrate-free diets containing only 40 or 50 gm. of protein for considerable periods, and the ordinary diets used by the writers and by Joslin in severe cases contain only some 50 or 60 gm. of protein. Furthermore, by far the principal energy value of all such diets is in the form of fat. Therefore, the only actual modification suggested by Newburgh and Marsh is a reduction of this protein ration by perhaps 20 gm., and the use of a fat and total calory allowance somewhat higher than that of ourselves and Joslin but lower than that of Naunyn, von Noorden, and Petré.

2. The theory of high fat diets seems to require some discussion. One misconception has been so prevalent in the older literature that it is no surprise to find it repeated by McLester¹⁸; namely, that in fasting the body fat is burned, therefore one might as well feed sufficient fat for the needs and thus save the nutritive condition. Von Noorden¹⁹ declared that fat (with the exception of butter, on account of its butyric acid) could be given without limit in diabetes and did not increase ketonuria. Others went so far as to assert that fat need not be withdrawn even in the presence of impending coma, because fat feeding does not increase fat combustion. Such suppositions defy old and new knowledge of both metabolism and diabetes. It should not be necessary to refer to the

early experiments from Pflüger's laboratory²⁰ showing that fat feeding is much more effective than fasting in driving glycogen out of the liver, or to the proof by Lusk²¹ that fat feeding increases fat combustion slightly but definitely, or to the marked acidosis, comparable to that of diabetes, produced in normal men by Landergren²² and Forssner²³ by means of fat feeding and deprivation of carbohydrate, or to the wholesale prevalence of diabetic coma which has always attended high fat diets. Ordinary fasting acidosis, when the body is burning its own fat, was far surpassed by the acidosis of fat feeding in Landergren and Forssner's experiments; and the effect of fasting in clearing up diabetic acidosis has been so striking that it has been adopted in practice by Naunyn, von Noorden and their followers in spite of theories to the contrary. The early investigations tending to establish acidosis as the result of a deficiency of carbohydrate in proportion to fat combustion have recently been extended by Woodyatt²⁴, Shaffer²⁵, and others²⁶.

All these data and those of Newburgh and Marsh are easily harmonized. When glycosuria is stopped by a diet very low in protein and carbohydrate, the influence toward checking acidosis is strong, and is only slightly counteracted by the feeding of 900 calories in fat, as the increase of fat metabolism thus produced is slight as compared with the fasting state. The diabetic free from glycosuria can endure larger quantities of fat than used by Newburgh and Marsh, as shown by von Noorden, Petrén and others, with no immediately serious acidosis, because even these quantities of fat elevate fat combustion only slightly. But on these low carbohydrate, high fat diets the liver and the body in general become stored with fat in preponderance over carbohydrate. The general overload of metabolism gradually lowers the carbohydrate tolerance; glycosuria ensues and wastes some of the scanty store of carbohydrate, and then the excess of fat in catabolism easily precipitates coma. The body then needs opportunity to burn off its overload of potentially toxic material. Although, as stated, the extra fat catabolism entailed by the rather low fat diet of Newburgh and Marsh is only slight as compared with fasting, it is also true that slight differences may be important at this stage, so that very few physiologists or physicians would endorse a proposal for fat feeding in impending

coma. It is furthermore obvious that the attempt to save body fat is contrary to the principle of undernutrition treatment, which is that the body weight must be reduced in proportion to the severity of the diabetes, as the only effectual means of keeping diabetic symptoms under control. From these theoretical considerations, it is to be anticipated that the immediate effect of moderate fat rations will be to impede more or less the usual benefits of undernutrition, and that the later result of slightly excessive fat diets will be downward progress varying in rapidity with the severity of the case.

3. These theoretical expectations appear to be fulfilled in the results of Newburgh and Marsh. It should be noticed first that their cases, like the usual unselected series, were mostly of mild type. Patients of 40 and 50 years and above predominated, and the minority of younger individuals, whether or not showing heavy glycosuria and acidosis at admission, were not seriously reduced in weight. For example, patient No. 27 in their second paper was only 18 years old, but weighed 155 pounds. Also, these patients soon became able to tolerate diets which disproved any extreme severity. For example, patient No. 21 was aged 22 years, but attained a blood sugar level of 0.12 per cent on a diet of 55 gm. protein, 30 gm. carbohydrate and 2400 calories. This is entirely comparable in protein and carbohydrate to the diets used by ourselves for cases of this grade, and in its excess of fat calories reproduces the feature of the Rockefeller Institute diets which proved so disastrous. A more severe case was that of patient No. 41, aged 18 years and weighing 90 pounds, whose diet began at 1000 calories and was increased only to 1600, while the blood sugar was never brought below 0.15 per cent. It may be suspected that other cases "not responding satisfactorily to treatment" would have responded more quickly and completely with a stricter application of undernutrition. On the other hand there is no record that any patient with severe diabetes and emaciation was ever made plump and strong.

As the effects of excesses in fat, however, are known to be slow, the principal harm is apt to be seen in the later history of any patients fed beyond their caloric tolerance. New-

burgh²⁷ has recently compiled the results of his experience from March 1, 1918 to Jan. 1, 1922 as follows:

Total number of patients observed.....	145
Refused treatment.....	8
Died in hospital.....	12
Lost from observation.....	23
<hr/>	
Discharged on diet after treatment.....	102
Living, Jan. 1, 1922.....	88 (86%)
Dead	14 (14%)

This is a good record, surpassing anything that would have been considered possible a few years ago, but the benefits seem readily explainable by the fact that the fat has only been relatively high in proportion to the other elements of the diet, and in severe cases the actual total ration has been kept low and undue attempts to build up the patient's weight have been avoided. There seems to be ground for the criticism of Joslin²⁸ that these results might have been improved by stricter observance of the undernutrition principle, and that forcing of the diet, so far as it has been undertaken, has increased the mortality. Taking account of the fewness of juvenile cases, and of those with extreme emaciation and other signs of great severity, the above statistics seem distinctly inferior to those of Joslin and also to our own results as presented in this paper. As time brings more severe cases to their clinic, we can see no escape offered by the method of Newburgh and Marsh from the dilemma which confronts all who treat diabetes, namely that the symptoms must either be allowed to persist or must be controlled at the expense of bodily weight and strength. Our personal impression also is that patients are better satisfied and more comfortable on diets lower in fat and slightly higher in protein and carbohydrate than those of Newburgh and Marsh.

It may be argued that various technical difficulties may modify clinical results, so that statistics cannot be taken strictly at their face value. This may be granted, and it is not the purpose to attack the work of Newburgh and Marsh, which finds its proper value and application in the debated question of the optimum balance between foodstuffs in the diabetic diet. It is a fact that some physicians have carried the fear of fat to an extreme of unnecessary starvation, and others have used so much protein or carbohydrate as to make toler-

ance for a living ration of total calories impossible. The work of Newburgh and Marsh will prove beneficial in correcting these mistakes. Two points, however, must still be emphasized. First, this work does not sanction the use of unlimited quantities of fat in the diabetic diet. Amazement must be felt at the shallow thinking displayed by the number of physicians and dietitians who have rushed into print in their respective mediums of publication, as if to announce some discovery that weak diabetics may be made well and strong by means of rich nutrition with fat. Second, this work has not overthrown the principle of undernutrition in diabetic treatment. This principle rests upon three supports; first, the animal experiments showing the dangers of fat; second, the clinical experiments showing the prompt evidences of injury from fat in sufficiently severe cases; third, the general statistics showing the improved results in all types of cases when diabetes is treated as a deficiency of total metabolism, requiring limitation of the total diet and body weight in proportion to the severity. None of these supports has been shaken in the slightest degree. So far as Newburgh and Marsh have contravened this principle, they appear to have met clinical mishaps. If extraneous excuses be made for these, they have at least not fattened a single severely diabetic patient, restored him to any lasting usefulness, or even kept him alive any long time on any high caloric ration. The one essential evil from which the undernutrition treatment gave relief was excessive fat feeding, and the benefits of such relief appear more strongly demonstrated today than they were at the time when this treatment was first proposed.

Conclusions.

The various clinical observations cannot be recapitulated in detail, but reference must be made to the tables and text.

The results of the present treatment in the milder types of diabetic cases, especially after the age of 40, may be called highly satisfactory, as most such patients can be maintained in comfort and usefulness, the dreaded complications of diabetes can be practically altogether avoided, and any downward progress can be prevented or reduced to such a minimum that the normal span of life can probably be completed, all at the price of simple precautions in diet.

Every dietetic treatment of the severe and progressive types of diabetes leaves much to be desired. The watchfulness and the privations in regard to diet are arduous; mistakes easily produce marked downward progress, which is impossible to retrieve; and in the later stages freedom from symptoms and prolongation of life are possible only at the cost of weakness, emaciation and invalidism. No form of diet has ever succeeded in restoring weight and strength to such patients, and attempts to do so have entailed downward progress and death in proportion to the overload imposed upon the total metabolism. The effects of fat are most easily overlooked, because early hyperglycemia and other symptoms are produced only in the severest cases, and later signs of injury in milder cases are so readily attributed to inevitable downward progress.

It is believed that the best results, practically as well as theoretically, are obtained when such cases are diagnosed early and treated from the outset by reduction of the total diet proportioned to the severity of the diabetes. All statistics appear to agree that such undernutrition maintains nutrition, strength and life longer and more beneficially than any attempts at forcing the total caloric intake, and also accomplishes an important prolongation of life and relief of some symptoms in the extreme stages in which a restoration of weight and strength is impossible under any method.

Whether the notoriously progressive tendency of the worst cases of diabetes, especially in the young, represents merely high susceptibility to injury from dietary excesses and from infections, and whether such downward progress may be completely prevented by an ideal degree of functional rest as indicated by continuous absence of hyperglycemia, is still not positively decided. A combination of clinical and pathological evidence makes this a plausible hypothesis, at least theoretically. The conclusion is warranted that practical treatment improves in its results in proportion as it approaches this theoretical ideal, and that if any element of spontaneous progressiveness exists in any typical diabetic cases it is no more than a minor factor.

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Table IV

TABLE IV

Case No.	Sex	Race	Occupation	Age at Admission	Date of Admission	Treatment before Admission	DURATION OF DIABETES				HEIGHT	BODY WEIGHT				Complications	Initial Treatment	Final Diet, Protein, CH and Total Cal.	Degree of Fidelity	Result		
												Ft.	In.	Pounds								
							Before Admission		After Admission	Total				At Admission	Final							
							Yr.	Mo.													Yr.	Mo.
1	F	Amer.	Schoolgirl	12	Mar. '19	None	..	1	34	2	11	4	11	88	73	53	Acidosis	Fasted 6 days, 20 prot. for 6 weeks	50-10-1000	Faithful	Severe case controlled by accurate diet.	
5	M	Heb.	Teacher	27	July '19	Never sugar free.	2	29	4	5	5	5	7	146	135	118	None	40 protein for 4 days.	70-20-1000	Partial	Lost from observation.	
6	M	Amer.	Lawyer	62	July '19	None	2	29	4	5	5	11	178	195	138	118	None	700 cal. for 2 weeks.	55-25-2000	Faithful	Chanced doctors. Retinal hemorrhages.	
7	M	Heb.	Saloon-keeper	50	July '19	Seldom sugar free	9	29	11	5	5	9	166	210	178	170	Brachial neuritis	700 cal. for 1 week.	50-60-1100	Unfaithful	Disappeared immediately.	
16	F	Amer.	Housewife	65	July '19	None	5	12	6	5	4	144	170	131	131	None	Hypernephroma	Unweighed	Unweighed	Faithful	Died suddenly in 1920, sugar-free.	
17	F	Amer.	Housewife	54	Nov. '19	None	4	26	6	2	4	124	96	68	56	Acidosis	None	Unweighed	Unweighed	Faithful	Living and well.	
23	M	Amer.	Schoolboy	15	Aug. '19	Partial. Constant glycosuria past 3 months	1	6	24	3	6	4	124	96	68	56	Acidosis	Fasted 1 week. Then 300 cal. for 1 mo.	40- 5- 700	Faithful	Died Aug. 1921 of inanition.	
24	M	Amer.	Salesman	27	Jan. '18	Partial at times none, occasionally	5	48	9	..	5	6	142	140	92	80	Intermittent neuritis. Pyelonephritis with calculi.	Fasted 4 days. Then 30 protein for 17 days.	50-10-1000	Faithful	In hospital. Severe diabetes, under control.	
25	M	Heb.	Liquor dealer	43	Aug. '19	Partial	2	24	4	..	5	2	136	117	85	73	None	Fasted 1 week. Then 200 cal. for 1 week	70-10-1500	Unfaithful	Severe diabetes. Abandoned treatment. Died Aug. 1920.	
26	F	Amer.	Housewife	55	Aug. '19	Partial	1	30	3	6	5	9	166	170	148	135	None	30 protein for 5 days.	80-25-1800	Faithful	Ceased weighing diet. Careless. Fairly well.	
31	M	Amer.	Artist	35	Aug. '18	Partial	2	28	4	4	5	5	141	137	90	84	Acidosis. Influenza	30 protein for 2 wks.	60-15-1000	Unfaithful	Severe diabetes. Broke diet. Died of influenza, Dec. 1919.	
34	M	Heb.	Silk mfr.	33	Aug. '19	Slight restrictions. Continuous glycosuria.	14	3	14	3	204	168	158	158	None	40 protein for 5 days.	80-25-1800	Fair	Stopped coming. Estimates diet. Appears well.	
36	F	Heb.	Housewife	55	July '19	Very lax.	5	30	7	6	5	7	157	274	210	202	Neuritis. Obesity	60 protein and 5 CH, 5 days	80-80-1500	Unfaithful	Careless. Overeats. Frequent glycosuria. Mild case.	
38	M	Heb.	..	45	Aug. '19	None	1	30	3	6	None	Low unweighed diet.	Unweighed	..	Symptom-free. Thinks he is cured.	
41	M	Amer.	Clerk	33	Aug. '19	Partial	1	21	2	9	5	5	141	115	87	67	Chronic endocarditis. Nephritis. Hypertension.	40 protein for 10-30-1700	Unweighed	Faithful	Severe diabetes. Died of nephritis in the Institute, June 1921.	
42	M	Heb.	Mfr.	58	Apr. '19	Lax. Continuous glycosuria.	4	45	7	9	5	8	164	210	137	126	None	500 cal. for 6 days.	70-30-1500	Faithful	Good health. Nearly normal blood sugar.	
43	M	Heb.	Furrier	45	Aug. '19	Lax	2	1	2	6	Heavy acidosis	30 protein. Frequent fasts	30- 0- 300	..	Abandoned treatment. Died in 6 months.	
44	M	Heb.	None	5	Aug. '19	Slight control.	..	8	29	3	1	3	9	50	44	42	35	Acidosis	20 protein for 4 days.	40-20- 450	Unfaithful	Changed doctors. Diet lax. Downward progress.
49	M	Heb.	Hotel clerk.	64	Sept. '19	None	12	28	41	4	5	2	173	119	112	112	Chronic nephritis	Unfaithful	50-10-1200	Unfaithful	Incurable breaking of diet.	
51	F	Amer.	Student	19	Sept. '19	Strict	2	28	4	4	147	142	134	134	None	60 protein and 50 CH for 3 days	Unweighed	Faithful	Excellent result. Finished college. Normal blood sugar. Never glycosuria.	
54	F	Amer.	Teacher	40	Sept. '19	Partial	1	28	3	4	5	4	139	150	120	67	None	35 protein, 5 CH and 400 cal. for 2 mos.	50-5-1000	Faithful	Severe diabetes. Invalid in hospital with mostly normal blood.	
56	M	Heb.	Hotel clerk	36	Sept. '19	Lax. Glycosuria	6	28	8	4	5	2	133	145	111	126	None	40 protein for 4 days.	60-40-1400	Faithful	Over weight. Estimates diet. Glycosuria recently.	
58	F	Amer.	Clerk	61	Oct. '19	None	2	6	27	4	8	150	..	None	Unweighed	Unweighed	Faithful	Well on unweighed diet.	
59	M	Heb.	Housewife	44	Jun. '20	None	8	19	9	7	None	Low unweighed diet.	Unweighed	Unfaithful	Abandoned treatment.	
60	M	Amer.	Lawyer	30	Oct. '19	Brief, partial	2	8	27	4	8	5	10	163	155	140	107	Pulmonary tuberculosis	40-15-400 for 10 days.	60-20-1400	Partial	Fair. Repeated lapses of diet. Diabetes now severe. Tuberculosis advancing.

61	M	Heb...	Saleman...	19 Oct.	'19	Brief, partial	4	1	27	6	5	6	132	165	143	134	None	40 protein for 3 days, 40 protein for 2 days	80-20-1200	Unfaithful	Abandoned diet. Died within 1 year. Not traced.
66	M	Cosia Rican	Real estate	59 Oct.	'19	Partial	3	5	6	157	178	140	136	Neuritis	Reduced total diet	70-60-1500	Faithful	
67	M	Heb...	Student	17 Jun.	'20	None	19	1	7	3	121	115	115	130	Boils	Unweighed	Partial	Boils disappeared. Follows unweighed diet. Excellent condition. Died Feb., 1920	
69	M	Heb...	Mfr.	59 Oct.	'19	Partial	15	5	5	5	5	5	149	157	122	110	Extreme arteriosclerosis. Gangrene. Pulmonary tuberculosis	40 protein, 5 CH for 10 days	70-25-1500	Faithful	
70	M	Norwegian	Carpenter	28 Oct.	'19	None	0	1	27	2	4	9	154	160	125	114	None	50 protein, 10 CH and 500 cal. for 5 days	70-25-2000	Faithful	Excellent. Later abandoned diet.
73	F	Heb...	Housewife	61 Oct.	'19	None	4	..	27	6	3	2	138	Chronic nephritis and hypertension. Arteriosclerosis	Low diet for 3 weeks	80-20-1000	Faithful	Changed treatment.
75	M	Heb...	None	4 Sept.	'19	Partial	2	..	28	4	3	2	26	22	None	25 protein for 5 days	40-5-800	Partial	Improved at first. Then occasional break of diet, with downward progress.
76	M	Heb...	Construction	27 Oct.	'19	Partial	2	..	8	2	8	5	158	167	128	112	Acidosis	30 protein for 3 weeks	30-5-500	Unreliable	Severe diabetes. Broke diet persistently. Abandoned treatment. Died in coma May, 1920.
77	M	Heb...	Tailor	48 Oct.	'19	Poor	1	27	3	3	5	10	171	200	150	143	Neuritis. Nephritis	40 protein, 5 CH for 5 days	40-15-700	Partial	Good. Mild case. Abandoned treatment.
78	M	Amer.	Business	44 Oct.	'19	Slight	0	3	27	2	6	9	164	174	151	130	None	900 cal. for 2 days	Unweighed	Faithful	Engaged in active business. Well except for tendency to hyperglycemia. Mild case.
84	F	Heb...	Authoress	53 Nov.	'19	Partial	12	..	26	14	2	5	157	150	133	126	Arteriosclerosis	40 protein and 20 CH for 10 days	80-15-1300	Faithful	Changed to unweighed diet. Fairly well.
85	M	Amer.	Physician	31 Nov.	'19	Hyperglycemia, no glycosuria	4	6	26	6	8	5	163	178	111	99	None	30 protein for 12 days	80-10-1100	Faithful	Severe case. Downward progress halted. Invalid in hospital.
88	M	Heb...	Clerk	32 Nov.	'19	Hyperglycemia, without glycosuria	2	..	5	2	5	6	145	162	140	95	Probably tuberculosis	300 cal. for 4 days	85-5-1200	Careless	Severe case. Died March, 1920.
90	M	Amer.	Chemist	46 Mar.	'20	Partial	18	..	22	19	10	5	152	200	133	122	Gangrene. Chronic nephritis. Retinitis	100 CH and 1500 cal. for 1 week	30-100-2000	Faithful	At work. Suffering only from nephritis and blindness.
94	F	Heb...	Housewife	47 Nov.	'19	Partial	4	..	26	6	2	4	11	220	169	133	None	50 protein, 20 CH for 2 weeks	55-25-1600	Faithful	Lax diet. Fair health.
97	M	Amer.	School	11 Nov.	'19	Partial	3	6	26	5	8	4	58	63	59	53	None	800 cal. for 2 days	85-30-1600	Occasional breaks of diet	Frequent breaks of diet. Slight downward progress.
98	M	Heb...	Tailor	44 Nov.	'19	Partial	0	6	26	2	6	5	136	180	127	122	None	40 protein, 5 CH for 2 days	...	Unfaithful	Mild case. Discharged for insubordination.
100	F	Heb...	Housewife	62 Nov.	'19	Partial	10	..	4	10	4	5	152	195	128	108	Gangrene. Arteriosclerosis. Apoplexy	30 protein, for 1 week. Then 40 protein, 5 CH for 1 week	80-10-1000	Faithful	Severe diabetes. Died Feb., 1920, of gangrene and apoplexy.
104	F	Amer.	Housewife	65 Nov.	'19	None	5	..	26	6	2	5	138	130	Cystitis	50 protein, 10 CH for 4 days	70-10-1800	Faithful	Good health under treatment
108	F	Heb...	Housewife	62 Dec.	'18	Partial	3	..	37	6	1	5	138	154	120	121	None	50 protein for 2 days	Unweighed	Mistakes	Good health on lax, unweighed diet with constant hyperglycemia.
111	M	Heb...	Jeweler	52 Dec.	'19	Partial	1	..	19	2	7	5	145	158	136	130	Cirrhosis of liver; probably syphilitic	Reduced unweighed diet	Unweighed	Unfaithful	Careless diet. Died July, 1921, of cirrhosis.

TABLE IV (Continued)

Case No.	Sex	Race	Occupation	Age at Admission	Date of Admission	Treatment before Admission	DURATION OF DIABETES				HEIGHT		BODY WEIGHT			Complications	Initial Treatment	Final Diet, Protein, CH and Total Cal.	Degree of Fidelity	Result			
							Before Admission		Total	HEIGHT		Ft.	In.	Pounds									
							Yr.	Mo.		Yr.	Mo.			Standard Normal	Before Admission						At Admission	Final	
112	F	Heb.	Housewife	49	Dec., '19	Partial	3	25	5	1	5	3	139	157	147	130	146	130	40 protein, 15 CH for 3 days	70-30-1400	Faithful...	Changed and abandoned treatment	
114	M	Amer.	Clerk	19	Dec., '19	Partial	1	2	1	2	5	7	136	113	113	88	113	88	20 to 30 protein with numerous fast days for 6 weeks	Unweighed.	Faithful...	Uncontrollable severity of diabetes. Died of inanition Jan., 1920.	
116	M	Heb.	Merchant	41	Dec., '19	Partial	0	3	25	2	4	5	9	164	178	163	146	136	35 protein, 40 CH for 3 days	Unweighed.	Faithful...	Mild case. Normal blood and good health.	
123	F	Ger.	School	9	Jan., '20	Partial	2	24	4	0	4	6	68	56	56	69	69	69	Average of 500 cal. for 3 months	40-5-800	Faithful...	Height 4 ft. 10 in. on Jan. 1, 1922. Excellent result. Weights diet.	
125	M	Amer.	Merchant	52	Jan., '20	Partial	0	3	8	0	11	5	11	178	112	112	90	90	Extreme arteriosclerosis and edema	40 protein, 5 CH for 4 days	Unweighed.	Faithful...	Hopeless severity. Died May, 1920.
126	M	Amer.	Mfr.	57	Jan., '20	Partial	30	24	32	0	5	7	157	218	178	108	108	108	60 protein, 10 CH for 3 days	Unweighed.	Faithful...	Healthy. Mild case.	
127	M	Heb.	Scientist	50	Jan., '20	None	1	24	3	0	5	8	162	190	190	160	160	160	500 cal. for 1 day	Unweighed.	Faithful...	Good health.	
131	M	Heb.	Tailor	35	Jan., '20	Partial	2	12	3	0	5	9	162	200	193	133	133	133	20 protein for 4 days	Unweighed.	Faithful...	Careless with diet. Feels well.	
132	F	Amer.	Home duties	22	Jan., '20	Partial	2	24	2	3	5	5	129	133	133	99	92	92	500 cal. for 1 day	Unweighed.	Faithful...	Feels entirely well and has married.	
134	F	Heb.	School	13	Jan., '20	None	0	4	24	2	4	11	80	76	76	76	76	76	20 protein for 4 days	Unweighed.	Faithful...	Careful with diet 6 months, then lax.	
135	M	Heb.	School	11	Jan., '20	None	0	1	24	2	1	4	5	65	144	215	190	182	50 protein for 3 days	Unweighed.	Faithful...	Recent temporary glycosuria. Height 5 ft. 1½ in. June, 1921.	
136	F	Heb.	Housewife	50	Jan., '20	None	0	6	24	2	6	5	4	144	215	190	182	182	400 cal. for 3 days	Unweighed.	Faithful...	Broke diet constantly. Now has glycosuria. Lost from observation. Living.	
137	F	Heb.	Housewife	45	Jan., '20	None	6	24	8	0	5	6	151	147	115	130	130	130	Low diet, unweighed	Unweighed.	Faithful...	Careless. Intermittent glycosuria.	
140	F	Amer.	Housewife	60	Feb., '20	Partial	12	23	13	11	5	0	133	151	116	113	113	113	60 protein, 20 CH and 800 cal. for 2 days	Unweighed.	Faithful...	Small excesses of diet. Health improved but poor.	
144	F	Amer.	Housewife	58	Feb., '20	Partial	2	23	3	11	5	6	152	210	145	122	122	122	50 protein, 10 CH for 6 days	Unweighed.	Faithful...	Normal blood sugar. Good health. Mild case.	
145	F	Heb.	Saleswoman	43	Feb., '20	None	1	23	2	0	5	6	147	137	101	91	91	91	Low diet, unweighed	Unweighed.	Faithful...	Lost from observation.	
149	M	Heb.	Mfr.	55	Feb., '20	Partial	10	9	10	9	5	6	153	143	112	107	107	107	Fasted 6 days. Then 30 protein for 10 days	Unweighed.	Faithful...	Severe diabetes. Died of tuberculosis Nov., 1920.	
150	M	Heb.	Mfr.	35	Feb., '20	None	0	5	12	1	5	5	131	118	99	98	98	98	50 protein, 25 CH for 8 days	Unweighed.	Faithful...	Severe diabetes. Abandoned treatment. Died Feb., 1921.	
151	F	Heb.	Housewife	37	Feb., '20	Partial	1	23	2	11	5	7	148	186	161	151	151	151	50 protein, 25 CH for 8 days	Unweighed.	Faithful...	Lost from observation.	

156	F	Amer.	Housewife	22	Feb.	'20	Partial	1	..	23	2/11	5	8	141	120	104	92	None	30 protein, 15 CH for 3 days	Faithful	Married. General loss of tolerance. Mistakes in diet. Three infections. Stopped treatment. Good. Return of symptoms later with carelessness. Stopped treatment.
158	F	Heb.	Housewife	66	Feb.	'20	None	15	..	23	16	11	5	2	138	200	142	134	Hypertension, Arterio-sclerosis. Glaucoma	20 protein for 8 days	Unweighed.
159	M	Heb.	Salesman	62	Feb.	'20	Partial	12	..	23	13	11	5	5	149	195	163	134	Heart disease. Arterio-sclerosis	800 cal. for 2 days.	Unweighed.
160	F	Amer.	Housewife	58	Feb.	'20	None	10	0	23	11	11	5	0	177	198	122	113	Gangrene of toe.	35 protein for 11 days	Faithful
161	F	Heb.	Author	50	Feb.	'20	Partial	5	0	23	6	11	5	6	152	177	150	133	None	Low calory diet.	Unweighed.
162	F	Heb.	Housewife	50	Feb.	'20	Partial	8	0	23	9	11	5	5	148	145	112	110	Retinitis.	Less than 500 cal. for 2 weeks	Unweighed.
166	M	Heb.	Child	2	Feb.	'20	Partial	0	3	3	0	27	30	25	24	Acidosis.	20 protein, 5 CH for 10 days. Then 40 protein, 10 CH for 9 days	Faithful
168	M	Heb.	Merchant	37	Feb.	'20	Partial	3	0	5	8	157	175	103	103	Acidosis.	Fasted for 9 days.	Unreliable
172	M	Heb.	Garage	32	Feb.	'20	Partial	1	0	22	2	10	5	7	149	157	133	130	None	50 protein, 20 CH and 900 cal. for 3 days	Faithful
173	F	Heb.	Housewife	36	Mar.	'20	Partial	3	0	2	3	2	5	2	129	155	108	69	Acidosis.	30 protein for 6 weeks. Did not respond to treatment	Faithful
174	F	Heb.	Clerk	42	Mar.	'20	Partial	2	0	22	3	10	5	2	133	115	86	75	Acidosis.	15 to 30 protein for 2 months	Faithful
175	F	Amer.	School	13	Mar.	'20	Partial	1	3	6	1	9	5	2	104	130	86	69	Acidosis.	20 to 30 protein for 1 month	Unreliable.
177	F	Heb.	Saleswoman	25	Mar.	'20	Partial	1	0	22	2	10	5	4	129	128	100	80	None	50 protein, 5 CH for 4 days	Faithful
180	M	Irish	Real estate	70	Mar.	'20	None	12	..	22	13	10	5	2	139	165	114	127	Gangrene of toe. Amputation. Cataract	60 protein, 10 CH for 2 weeks	Faithful
184	F	Heb.	School	11	Mar.	'20	None	0	10	9	1	7	4	5 1/2	63	70	53	50	Acidosis.	15 protein for 8 weeks, with 8 fast days	Faithful
187	F	Amer.	School	14	Mar.	'20	None	0	10	17	1	5	5	0	96	98	75	74	Pulmonary tuberculosis.	20 protein for 9 days	Unfaithful.
196	F	Heb.	School	17	Mar.	'20	None	0	1	22	1	11	5	3	120	121	121	116	Boils	1000 cal. for 1 day.	Faithful
200	M	Heb.	Mfr.	53	Mar.	'20	None	11	0	21	12	9	5	3	142	142	121	119	Endarteritis	45 protein, 5 CH for 5 days	Faithful while under treatment
205	F	Amer.	School	13	Mar.	'20	None	0	3	16	1	5	4	11	89	67	66	63	None	Fasted 4 days. 20 protein for 4 days	Partial
208	M	Amer.	Mfr.	43	Apr.	'20	Partial	1	0	21	2	9	5	3	139	163	118	113	None	30 protein, 10 CH for 3 days	Faithful
210	F	Heb.	Merchant	35	Mar.	'20	Partial	5 wk s.	Heart disease	Low unweighed diet	Unweighed.
211	M	Amer.	Merchant	60	Mar.	'20	None	5	0	17	6	5	5	4	145	140	116	108	None	Broke diet continued daily	Unweighed.
212	F	Heb.	Housewife	63	Mar.	'20	Partial	10	0	22	11	10	5	6	152	160	130	125	Chronic nephritis. Hypertension. Retinitis. Senile dementia	40 protein, 5 CH for 12 days	Faithful
214	F	Amer.	School	26	Apr.	'20	Partial	2	0	5	2	5	5	6	136	116	95	92	None	1400 cal. for 6 days.	Unreliable.
215	M	Heb.	Chaufeur	22	Apr.	'20	Lax; partial	4	0	20	5	8	5	8	146	121	131	105	None	30 protein for 11 days	Faithful
216	M	Heb.	Tailor	52	Apr.	'20	None	6	0	21	7	9	5	6	153	186	160	..	None	Low unweighed diet.	Partial.

TABLE IV (Continued)

Case No.	Sex	Race	Occupation	Age at Admission	Date of Admission	Treatment Before Admission	DURATION OF DIABETES				HEIGHT		BODY WEIGHT				Complications	Initial Treatment	Final Diet, Protein, CH and Total Cal.	Degree of Fidelity	Result	
							Before Admission		Total	Ft. In.		Pounds										
							Yr.	Mo.		Yr.	Mo.	Standard Normal	Before Diabetes	At Admission	Final							
218	F	Amer.	Housewife	75	Apr., '20	Partial	5	0	3	5	3	5	4	144	260	234	223	Extrem obesity and heart disease	60 protein, 15 CH for 5 days	80-50-1200	Faithful	Died suddenly June, 1920. Sugar-free.
219	F	Amer.	Housewife	41	Apr., '20	Free from glycosuria at first. Later careless	8	0	3	8	3	5	5	143	125	93	91	Acidosis	20 protein for 6 weeks	60 protein	Faithful	Abandoned treatment. Died June, 1920. Severe case.
220	M	Heb.	Salesman	55	Apr., '20	Partial	6	0	21	7	9	110	148	129	148	110	Psychosis	Low unweighed diet.	Unweighed.	Faithful	Good physical health.	
221	F	Heb.	Housewife	23	Apr., '20	Partial	0	1	5	0	6	5	5	129	148	110	102	None	35 protein for 1 week	160-15-1400	Faithful	Mild diabetes. Abandoned treatment. Died Sept., 1920.
225	M	Amer.	Banker	55	Apr., '20	Partial	3	0	16	4	4	5	11	178	200	129	111	Probably pulmonary tuberculosis	30 protein, 10 CH for 8 days	60-30-1400	Faithful	Abandoned diet. Died August 1, 1921.
226	F	Heb.	Home duties	61	Apr., '20	Careless	8	0	1/2	8	0	Acidosis. Gangrene of toe	40 CH	40 CH	Faithful	Died coma, April, 1920.
228	F	Heb.	Housewife	64	Apr., '20	None	9	0	1	9	1	5	7	157	175	125	102	Chronic nephritis. Arteriosclerosis. Hypertension	35 protein for 5 weeks, 40 protein and irregular fasts for 2 weeks	55-5-1000	Partial	Broke diet. Died July, 1921. Severe diabetes.
229	F	Heb.	School	8	Apr., '20	Partial	3	6	21	5	3	3	7	40	36	41	35	None	20 protein for 7 days	40-5-800	Fair	Frequent hyperglycemia. Barely holds own.
230	M	Heb.	Mfr.	20	Apr., '20	Partial	0	1	16	1	5	5	8	146	146	133	131	None	50 protein, 10 CH for 5 days	70-20-1400	Faithful	Progressed to severe state by breaking diet. Died 1921.
232	F	Heb.	Housewife	40	Apr., '20	Partial. Glycosuria most of time	1	..	16	2	4	5	6	147	150	122	114	Hypertension	40 protein, 40 CH for 5 days	70-40-1600	Faithful	Followed diet 3 months. Lost from observation. Living.
234	M	Amer.	Clerk	26	Apr., '20	Sugar-free first 2 years. Glycosuria recently	3	..	21	4	9	5	11	163	165	154	122	None	Unweighed. Total dietary restriction	Unweighed.	Faithful	Glycosuria absent on unweighed diet.
235	M	Amer.	Hotel-keeper	45	Apr., '20	Careless, lax	3	6	21	5	3	5	10	171	194	146	139	None	30 protein, 10 CH for 11 days	60-5-1200	Careless	Abandoned treatment.
236	F	Heb.	Housewife	45	Apr., '20	None. Constant glycosuria	6	..	21	7	9	200	166	..	Unweighed	Unweighed	Unweighed.	Partial	Lost from observation.
239	F	Amer.	Housewife	57	Apr., '20	Partial	4	6	21	6	3	5	5	148	165	100	150	Furuncles. Cholecystitis	70 protein, 15 CH for 2 weeks	75-40-2000	Careless	Changed doctors. Living and well.
241	M	Amer.	Salesman	37	Apr., '20	None	1	..	21	2	9	5	10	167	245	225	190	Pruritus	1200 cal. for 1 day	Unweighed.	Faithful	Good physical health.
242	F	Amer.	Housework	69	May, '20	Partial	4	..	20	5	8	5	8	162	165	135	125	Carbuncles	Low unweighed diet.	Unweighed.	Partial	First indifferent, then abandoned treatment.
243	F	Heb.	Dentist	47	May, '20	Half-hearted. Intermittent glycosuria	20	5	..	6	8	5	5	146	210	155	151	Hypertension	3 fast days	70-40-1200	Faithful	Followed diet 2 months. Changed treatment.
244	F	Heb.	Housewife	48	May, '20	Practically none	6	..	20	7	8	5	7	155	178	136	101	Hypertension. Goitre	40 protein, 30 CH for 6 days. Then 10 to 20 protein for 3 weeks	55-5-1000	Faithful	Severe diabetes. Accurate diet 1 year. Lost from observation.
246	F	Amer.	Housewife	24	May, '20	Partial	0	2	20	1	10	5	3	123	110	91	86	None	30 protein, 30 CH for 3 days	70-40-1500	Partial	Accurate diet for 1 year. Then careless. Living.
247	F	Heb.	Teacher	27	May, '20	Partial	4	20	..	5	8	5	0	118	110	110	108	None	70 protein, 60 CH for 2 days	Unweighed.	Unreliable	Careless. Mild case.
248	M	Amer.	Clerk	42	May, '20	None	2	..	10	2	0	5	7	154	145	118	100	Neuritis	40 protein for 4 days	50-5-900	Unreliable	Abandoned treatment. Died March, 1921.

251	F Heb..	Housewife...	56	May, '20	Glycosuria most of time	8	..	20	9	8	5	6	152	150	123	121	None	50 protein, 10 CH for 10 days	10 CH 70-30-1400	Faithful...	Faithful for short time. observation.	Lost from
258	F Amer.	Housewife...	62	May, '20	None	0	4	20	2	0	5	9	166	191	162	155	Pruritus	Low unweighed diet.	Unweighed..	Faithful...	Glycosuria cleared. Followed diet.	
259	F Heb..	Housewife...	41	May, '20	Restricted CH	0	2	20	1	10	5	2	133	166	141	116	Hypertension.	Hy- 50 protein, 20 CH for 5 days and 500 cal. for 5 days	75-55-1800.	Faithful...	No hyperglycemia. Excellent fidelity and health.	
262	M Heb..	Merchant...	62	May, '20	Restricted CH	5	..	20	6	8	5	10	172	195	164	157	Hypertension	60 protein, 20 CH for 2 days	80-40-1800.	Faithful...	Mild case. Followed diet 2 months. Lost from observation.	
265	F Heb..	Housewife...	49	May, '20	Disregarded diet.	13	..	18	14	6	5	8	159	198	130	105	Gangrene.	25 protein, 5 CH for 3 weeks	40-10-700..	Untrust- worthy	Abandoned treatment. Died Nov., 1921.	
266	F Heb..	Housewife...	45	May, '20	Constant glyco- suria	6	..	20	7	8	5	7	155	170	140	131	Neuritis.	30 protein, 10 CH for 4 days	70-50-1000.	Partial...	Faithful. Under treatment 5 months. Not seen since.	
267	F Amer.	Housewife...	68	May, '20	None	9	20	..	10	8	5	9	166	160	148	143	Cataracts.	40 protein, 10 CH for 8 days	70-30-1500.	Faithful...	Cleared of glycosuria and hyper- glycemia. Not seen since.	
273	F Heb..	Housewife...	57	June, '20	Constant glyco- suria	8	..	20	9	8	145	142	None	Fasted 4 days. Then 30 protein for 4 days	60-20-800..	Faithful...	Lost from observation.	
274	M Heb..	School...	13	June, '20	None	0	1	19	1	8	5	1	99	120	98	96	None	30 protein, 30 CH for 1 day	60-35-1600.	Faithful...	Excellent. Occasional hypergly- cemia.	
280	F Amer.	Home duties.	74	June, '20	Partial. Free from glycosuria most of time	1	6	19	3	1	5	10	170	200	180	174	None	Low unweighed diet.	Unweighed..	Mistakes.	Makes mistakes. Never has glyco- suria.	
283	M Heb..	Clerk...	29	June, '20	None	1	..	1	1	1	5	10	153	150	120	..	Acidosis.	40 CH	40 CH	Faithful...	Changed doctors. Died in coma June, 1920.	
286	F Amer.	Housewife...	55	June, '20	Partial	5	..	2	5	2	5	8	162	165	84	84	Acidosis.	Did not respond to 40 protein treatment	40 protein	Doubtful.	Broke diet. Died in coma July, 1921.	
287	M Heb..	Artist...	49	June, '20	Glycosuria most of time	13	..	19	14	7	5	10	171	195	165	150	Neuritis.	40 protein, 10 CH for 7 days	50-5-900..	Unreliable.	Changed doctors.	
288	M Heb..	Insurance...	50	June, '20	Restricted CH	14	..	20	15	8	5	5	149	184	151	137	None	40 protein, 10 CH for 2 days	Unweighed..	Partial...	Careful. Never glycosuria.	
290	F Heb..	Housewife...	48	June, '20	Restricted sugar and starch only	0	3	20	1	11	5	10	166	192	159	154	Hypertension.	40 protein for 3 days	65-20-900..	Faithful...	Followed diet 1 year. Good result.	
291	F Heb..	Housewife...	49	June, '20	Partial	6	..	19	7	7	5	7	155	170	115	102	Hypertension.	30 protein, 10 CH for 9 days	50-10-1000.	Faithful...	Excellent fidelity and health.	
294	M Heb..	Insurance...	44	June, '20	Practically none.	10	..	19	11	7	5	6	150	212	182	175	Neuritis.	Low unweighed diet.	Unweighed..	Unreliable.	Careless. Changed doctors. Re- tinitis and gangrene.	
295	F Heb..	Housewife...	53	July, '20	Partial	6	..	18	7	6	5	4	144	200	141	133	Gall-stones	40 protein, 10 CH for 4 days	70-25-1700.	Partial...	Follows diet inaccurately. Alive.	
300	F Heb..	Housewife...	60	July, '20	Only CH restrict- ed. Glycosuria most of time	1	6	18	3	0	5	1	135	145	128	118	Hypertension.	40 protein, 15 CH for 8 days	70-25-1700.	Faithful...	Developed psychosis. Abandoned treatment.	
301	M Amer.	Druggist...	58	July, '20	CH restricted.	1	..	5	1	5	5	6	153	200	153	124	Hypertension.	Complete fast 8 days	70-30-1800.	Untrust- worthy	Broke diet. Died Dec., 1920.	
304	M Amer.	Structural worker	45	July, '20	Constant glyco- suria	2	..	8	2	8	6	0	183	210	126	110	Pulmonary tuberculosis.	40 protein for 17 days	60-15-1300.	Faithful...	Abandoned diet. Died March, 1921.	
305	M Heb..	Merchant...	49	July, '20	Practically none.	7	..	18	8	6	5	8	161	190	162	152	Boils	60 protein, 10 CH for 5 days	30-30-1700.	Faithful...	Good fidelity and health.	
307	M Heb..	Mfr.	65	Aug., '20	Restricted CH. Glycosuria most of time	4	..	17	5	5	5	11	178	207	168	157	Hypertension.	Hyper- 40 protein, 10 CH for 11 days	70-30-1800.	Faithful...	Remains free of glycosuria.	
254	M Heb..	Salesman...	64	May, '20	Glycosuria most of time	15	..	3	15	3	5	6	153	187	144	129	Pulmonary tuberculosis.	30 protein for 3 weeks	40-5-600...	Faithful...	Died of tuberculosis Aug., 1920.	
312	M Heb..	Mechanic...	56	Aug., '20	Glycosuria past 2 years	6	..	16	7	5	5	11	178	206	136	133	Neuritis.	40 protein for 5 days	60-10-1400.	Faithful...	Partially faithful. Tries to do heavy labor. Fair result.	
314	M Amer.	Botanist...	43	Aug., '20	Constant glyco- suria for 11 years	14	..	16	15	4	5	10	169	170	129	120	Acidosis.	30 protein for 4 weeks	50-20-1200.	Faithful...	Not on weighed diet. Glycosuria greater part of time.	
315	F Heb..	Housewife...	32	Aug., '20	Restricted CH	1	..	16	2	4	5	4	132	143	92	88	None	30 protein for 8 days	50-20-1200.	Faithful...	Followed diet 1 year. Remained in good condition.	

TABLE IV (Continued)

Case No.	Sex	Race	Occupation	Age at Admission	Date of Admission	Treatment Before Admission	DURATION OF DIABETES				HEIGHT		BODY WEIGHT				Complications	Initial Treatment	Final Diet, Protein, CH and Total Cal.	Degree of Fidelity	Result	
							Before Admission	After Admission	Total	Ft.	In.	Pounds										
												Standard Normal	Before Admission	Final								
															Yr.	Mo.						Yr.
317	M	Heb.	Clerk	27	July, '20	Diet increased in attempt to prevent loss of weight	2 weeks	17	1	5	5	6	142	158	114	111	None	1100 cal. for 1 day.	60-20-1800	Faithful	Hyperglycemia, but no glycosuria.	
318	F	Heb.	Housewife	39	Aug., '20	None	3	16	4	4	5	3	132	160	120	112	Cerebro-spinal syphilis.	40 protein, 10 CH for 2 weeks	80-10-1200.	Faithful	Became totally insane. Diabetes disregarded. Died.	
319	F	Heb.	Housewife	44	Aug., '20	None	0	8	16	2	0	5	7	151	180	170	150	Neuritis. Hysteria.	40 protein, 20 CH for 1 week	70-20-1200.	Untrustworthy	Abandoned treatment immediately.
320	F	Heb.	Housewife	37	Aug., '20	Only CH restricted	3	16	4	4	5	2	129	125	104	98	Boils.	30 protein for 2 days	Unweighed.	Faithful	Mild case. Good result.	
321	M	Heb.	Merchant	48	Aug., '20	Low protein diet. Intermittent glycosuria	8	16	9	4	5	4	144	182	168	161	Thrombosis of femoral vein	50 protein, 10 CH for 7 days	Unweighed.	Broken diet.	Careless with diet.	
324	M	Heb.	Merchant	61	Aug., '20	None	23	16	24	4	5	9	167	202	149	121	Gangrene. Acidosis. Amputation of left leg	10 protein for 7 days. Then 30 protein for 2 weeks	Unweighed.	Faithful	Fair tolerance. Observes diet poorly	
328	M	Amer.	Soldier	26	Aug., '20	Restricted to prevent glycosuria. Constant glycosuria past 4 months	2	17	3	5	5	6	142	155	111	81	None	40 protein for 20 days	65-20-1600	Partial	Free of glycosuria and hyperglycemia for 1 year. Then abandoned diet. Living.	
329	F	Ger.	Housewife	56	Aug., '20	Restricted CH	1	16	2	4	5	6	152	245	170	143	Sinusitis. Neuritis.	40 protein for 7 days	65-15-1300	Faithful	Free of glycosuria. Good result.	
331	M	Amer.	School	7	Sept., '20	Partial	0	5	15	2	8	4	0	53	52	43	41	None	35 protein, 35 CH for 1 day	70-50-1000.	Unfaithful	Broke diet when opportunity afforded. Scarlet fever lowered tolerance. Died.
333	M	Amer.	Farmer	60	Aug., '20	None	12	16	13	4	5	2	139	180	157	120	Gangrene. Amputation of leg April, 1921. Hypertension	40 protein and 5 CH for 3 days	Unweighed.	Faithful	Careless. Died of apoplexy Nov. 22, 1921.	
334	M	Heb.	Mfr.	29	Sept., '20	None. Careless	5	15	6	3	5	7	146	165	162	163	None	40 protein for 1 day	Unweighed.	Partial	Glycosuria rare. Fair result.	
335	F	Heb.	Housewife	64	Oct., '20	Glycosuria most of time	7	1	7	1	5	6	152	200	162	157	Acidosis. Gangrene. Hypertension. Psychosis	40 CH	30 protein for 10 days. Then 5 protein daily for 2 months, with 22 fast days	30-2-500 and 10 CH	Faithful	Died gangrene Nov., 1920.
336	F	Amer.	School	13	Sept., '20	Partial	1	15	2	3	4	9½	80	84	61	46	Acidosis.	30 protein for 12 days. Then 5 protein daily for 2 months, with 22 fast days	12-30-2-500	Faithful	Followed diet 1 year. Abandoned diet. Invalid. Living.	
337	M	Amer.	School	18	Sept., '20	Restricted diet to prevent glycosuria. Constant glycosuria past 4 months	3	16	4	4	5	6	132	120	95	91	Bronchitis.	40 protein for 10 days. Then 10 protein for 2 weeks	65-15-1000.	Faithful	Excellent fidelity and health.	
339	F	Amer.	School	12	Sept., '20	Partial	0	8	16	2	0	4	8	75	80	72	73	Boils.	50 protein, 40 CH for 5 days	60-15-1600	Faithful	Good fidelity and health.
340	F	Amer.	School	18	Sept., '20	CH restricted to 50 grams sugar and starch. Glycosuria most of time recently	1	16	2	4	5	7	134	136	122	119	None	40 protein for 5 days	70-30-1800.	Faithful	Follows diet. Good result.	
343	F	Amer.	Housewife	59	Sept., '20	Only restricted sugar and starch. Glycosuria most of time recently	13	16	14	4	5	10	170	196	145	118	Hypertension.	40 protein for 12 days	70-15-1500.	Faithful	Accurate diet. Tendency to hyperglycemia.	

345	M	Amer.	Physician	54	Sept., '20	None	20	16	21	4	167	5	9	205	188	1	None	60 protein for 5 days	Unweighed.	Faithful.	Partially faithful. Feels well.	
346	M	Heb.	Saleman	38	Oct., '20	None	0	2	15	1	5	5	1	131	185	148	136	None	60 protein, 5 CH for 70-20	Unfaithful.	Abandoned treatment.	
347	F	Heb.	Housewife	50	Oct., '20	None	7	15	8	3	5	2	138	153	106	104	Neuritis. Hypertension.	40 protein for 9 days	50-5-800	Faithful.	Gave up treatment.	
350	M	Amer.	Saleman	30	Oct., '20	Diet increased in attempt to prevent loss of weight	0	9	14	1	11	5	6	145	178	126	132	None	40 protein, 5 CH for 70-20-1700	Faithful.	Good result for 7 months, then changed treatment. Living.	
352	M	Ger.	Insurance	60	Oct., '20	None. Glycosuria since onset	27	6	27	6	5	5	149	200	139	129	Cataracts, Retinitis, Hypertension	30 protein for 4 days	70-30-2000	Faithful	Died of Nephritis April, 1920.	
353	M	Amer.	Banker	50	Oct., '20	None	1	15	2	3	5	10	172	165	153	147	Neuritis. Gastritis	30 protein for 5 days	40-5-800	Unfaithful	Gave up treatment. Living.	
355	F	Amer.	Housewife	58	Oct., '20	Partial. Lax	8	15	9	3	5	6	158	171	121	108	Hypertension. Angina pectoris	30 protein for 2 1/2 weeks	75-15-2000	Faithful	Changed treatment. Living.	
356	M	Heb.	Grocer	33	Oct., '20	Partial at times	2	15	3	3	3	5	4	137	168	115	113	None	30 protein for 19 70-20-1800	Faithful	Not heard from.	
359	F	Heb.	Housewife	54	Nov., '20	Partial	2	14	3	2	5	4	144	168	135	131	Hypertension. Neuritis	20 protein for 4 days	60-30-1700	Faithful	Mistakes. Faithful in general.	
360	F	Heb.	Housewife	36	Oct., '20	None	5	15	6	3	5	4	136	180	125	122	Boils.	40 protein for 2 days	65-20-1700	Faithful	Fair result.	
361	F	Heb.	Housewife	44	Oct., '20	Partial	3	15	4	3	4	9	122	202	166	155	None	40 protein for 2 1/2 weeks	75-30-1600	Untrustworthy	Keeps free of glycosuria.	
362	F	Heb.	Housewife	52	Oct., '20	None	2	15	3	3	3	5	2	138	162	120	87	Gangrene, Acidosis, Nephritis	30 protein for 3 weeks	40-5-700	Faithful	Ignorant patient. Gave up treatment.
363	M	Amer.	Child	4	Nov., '20	Partial	0	3	14	2	5	3	5	37	35	29	28	None	20 protein, 5 CH for 40-15-800	Faithful	Poor result. Hyperglycemia without glycosuria most of time.	
366	F	Heb.	Housewife	37	Nov., '20	Restricted CH	3	14	4	2	5	5	140	165	142	119	Gall-stones	30 protein for 2 weeks	Unweighed	Faithful	Changed doctors.	
368	F	Heb.	Housewife	45	Nov., '20	Restricted CH. Intermittent glycosuria	5	14	6	2	5	3	139	185	134	128	Hypertension	40 protein for 7 days	70-20-1700	Faithful	Excellent result. Follows diet.	
369	M	Heb.	Merchant	47	Nov., '20	None	4	14	5	2	5	6	152	170	144	140	Neuritis	40 protein, 5 CH for 30-10-1300	Faithful	Faithful	Treats self. Sugar-free.	
370	F	Heb.	Housewife	52	Nov., '20	Glycosuria most of time	12	14	13	3	5	3	141	190	149	142	Carbuncles, Gall-stones, Neuritis	40 protein for 8 days	50-10-1200	Unfaithful	Abandoned treatment.	
371	M	Amer.	Teacher	31	Nov., '20	Partial. Glycosuria most of time	3	11	3	11	6	0	174	175	137	117	Infected toe	40 protein for 28 50-20-1700	Faithful	Faithful	Kept free of hyperglycemia with good result 10 months. Abandoned treatment. Died coma, Oct., 1921.	
374	F	Heb.	Housewife	38	Nov., '20	Restricted CH. Intermittent glycosuria	1	14	2	2	5	4	136	172	131	125	Alveolar abscess	40 protein, 20 CH for 60-20-1200	Partial	Partial	Mistakes.	
375	M	Ger.	Grocer	34	Nov., '20	Partial	1	14	2	2	5	6	145	206	280	266	None	70 protein, 5 CH for 125-60-2500	Faithful	Faithful	Good fidelity and health.	
376	F	Heb.	Housewife	54	Dec., '20	None	3	13	4	1	5	4	144	157	137	130	Hypertension. Neuritis	40 protein for 3 60-10-1100	Faithful	Faithful	Fair. Remains free of glycosuria.	
380	F	Heb.	Midwife	48	Dec., '20	Partial	0	1	13	1	2	5	1	133	150	139	122	Neuritis. Hypertension.	40 protein, 10 CH 85-50-1200	Faithful	Faithful	Excellent. Follows accurate diet.
381	F	Aust.	Child	2	Dec., '20	None	0	3	3	0	6	2	11 1/2	33	27	20	19	None	10 protein, 2 CH for 12-2-350	Faithful	Faithful	Free from hyperglycemia. Parents ignorant. Fed child. Died coma, Feb., 1921.
382	F	Amer.	Housewife	24	Dec., '20	Partial. Poor	1	6	13	2	7	5	3	123	135	103	95	None	30 protein for 5 40-5-500	Unfaithful	Unfaithful	Severe diabetes. Abandoned treatment. Became pregnant. Died Dec., 1921.
384	F	Amer.	School	16	Dec., '20	Partial	0	3	13	1	4	5	3 3/4	120	104	109	91	None	30 protein for 7 days 50-15-1200	Unfaithful	Unfaithful	Poor result. Broke diet. Gave up treatment.
385	F	Heb.	Housewife	20	Nov., '20	Good. Free of glycosuria until recently	1	14	2	2	5	6	133	134	129	116	None	30 protein for 7 days 75-30-2000	Faithful	Faithful	Excellent result. Normal blood sugar on weighed diet.	
391	F	Heb.	Housewife	47	Nov., '20	Glycosuria constant	3	14	4	2	5	5	146	136	123	120	Hypertension	Unweighed	Unweighed	Partial	Free of glycosuria.	
393	M	Span.	Banker	53	Nov., '20	Glycosuria most of time	8	14	9	2	5	10	172	230	183	180	Neuritis	50 protein, 15 CH 80-30-1600	Faithful	Faithful	Lives in South America. No report.	

TABLE IV (Continued)

Case No.	Sex	Race	Occupation	Age at Admission	Date of Admission	Treatment before Admission	DURATION OF DIABETES				HEIGHT		BODY WEIGHT				Complications	Initial Treatment	Final Diet, Protein, CH and Total Cal.	Degree of Fidelity	Result		
							Before Admission		After Admission	Total	Ft. In.	Pounds	Standard Normal	Before Admission	at Admission	Final							
							Yr.	Mo.														Yr.	Mo.
							Yr.	Mo.	Yr.	Mo.	Yr.	Mo.	Yr.	Mo.	Yr.	Mo.						Yr.	Mo.
396	M	Amer.	Banker	56	Nov., '20	None	1	14	2	2	6	0	184	236	186	186	186	Melancholia	40 protein, 10 CH for 2 weeks	80-60-2800	Faithful	Fair health restored.	
402	F	Heb.	Housewife	49	Oct., '20	Glycosuria intermittent. More frequent recently	6	12	1	6	5	3	139	165	115	115	115	Hypertension. Manic depressive psychosis	30 protein for 2 days	70-20-1700	Faithful	Developed psychosis. Died Oct., 1921.	
403	M	Heb.	School	12	Oct., '20	Sugar-free first 6 months. Then broke diet	0	9	15	2	0		89	80	79		80	79	None	20 protein, 10 CH for 4 days	50-10-1000	Unfaithful	Broke diet constantly. Discharged.
404	M	Amer.	Banker	81	Dec., '20	Partial	1	13	1	1	5	10	172	200	195	195	195	None	Reduced unweighed diet	Unweighed	Careless	Improved vigor.	
406	M	Amer.	Mfr.	61	Dec., '20	Restricted to pre-diabetic glycosuria	0	11½	13	1	2	5	4	145	152	141	141	141	None	40 protein, 5 CH for 9 days	85-50-2600	Faithful	Normal blood sugar on weighed diet. Good result.
409	M	Heb.	Merchant	32	Dec., '20	Practically none.	3	13	4	1	5	2	131	138	108	108	108	108	None	30 protein for 12 days		Unfaithful	Broke diet incorrigibly. Discharged.
410	F	Heb.	Child	4	Jan., '21	None	0	4	6	0	10	3 ¾	36	37	28	26	26	Acidosis	30 protein, 5 CH for 6 days	50-10-900	Faithful	Abandoned treatment. Died July 1921.	
413	F	Amer.	Home Clerk	25	Jan., '21	No glycosuria	0	4	12	1	4	5	3	125	116	94	104	104	None	30 protein for 5 days	70-20-1600	Faithful	Excellent fidelity and health.
422	F	Heb.		23	Jan., '21	Good for first year. Since then occasional glycosuria	2	12	3	0	5	0	115	140	101	99	99	None	20 protein for 2 months, with 12 fast-days	40-5-900	Faithful	Good.	
423	M	Amer.	Automobile mechanic	33	Jan., '21	Poor. Ins.	2	5	2	5	5	5	141	155	98	87	87	None	30 protein for 1 month	150-10-1100	Unfaithful	Abandoned treatment. Died June 11, 1921.	
425	M	Heb.	Insurance	54	Jan., '21	Indifferent	8	12	9	0	5	3	142	153	136	130	130	Chronic alcoholism	60 protein, 10 CH for 8 days	Unweighed	Faithful	Careless in diet. Living.	
431	F	Heb.	Housewife	32	Jan., '21	None	5	10	1	4	5	9	123	200	157	149	149	Neuritis	40 protein for 6 days	75-25-1700	Unfaithful	Gave up treatment.	
432	M	Amer.	Watchman	54	Jan., '21	None	0	6	10	1	4	5	9	167	178	113	103	103	Gall-stones. Pancreatic calculi?	30 protein for 2 weeks	250-10-1200	Unfaithful	Discharged diet. Died Nov. 6, 1921.
433	M	Heb.	Merchant	51	Jan., '21	Ignorant, careless.	4	12	5	0	5	2	139	150	150	118	118	Sciatica	30 protein for 6 days	65-10-1500	Faithful	Keeps free of glycosuria. Blood sugars fairly low	
436	M	Amer.	Minister	47	Jan., '21	Partial. Overate.	0	7	12	1	7	5	9	166	170	136	103	103	Neuritis	30 protein for 2 days	70-25-1800	Faithful	Mistakes. Downward progress.
437	F	Heb.	Housewife	57	Jan., '21	Practically none.	9	12	10	0	4	11	131	210	131	130	130	Neuritis	30 protein for 5 days	65-20-1000	Unreliable	Abandoned treatment.	
438	F	Amer.	Housewife	55	Jan., '21	Glycosuria most of time	10	12	11	0	5	0	133	200	136	132	132	Cataracts. Neuritis	30 protein for 10 days	45-10-600	Unfaithful	Abandoned treatment.	
439	M	Amer.	Hardware	31	Jan., '21	None	4	12	5	0	5	7	149	140	74	70	70	Pancreatic calculi?	25 protein for 2 weeks	260-10-1000	Faithful	Partial co-operation. Glycosuria intermittent.	
441	F	Amer.	Housewife	70	Feb., '21	Intermittent glycosuria	12	11	12	11	5	4	144	180	125	117	117	Hypertension. Angina	30 protein, 3 CH for 10 days	75-25-2000	Faithful	Improved. No glycosuria. Mistakes. Good result.	
443	M	Irish	School	10	Feb., '21	None	0	2	11	1	1	4	5	64	80	52	64	64	None	30 protein for 3 days	80-40-1900	Partial	Partially faithful. Occasional breaks of diet. Height 4 ft. 7½ inches Jan. 1, 1922.
447	M	Amer.	Dentist	35	Feb., '21	Partial	1	11	1	11	5	9	162	145	138	127	127	None	1600 cal. for 4 days	Unweighed	Faithful	Normal blood sugar. Good result.	
448	M	Amer.	Architect	36	Feb., '21	Restricted diet	5	5	5	5	5	8	157	170	108	108	104	Pulmonary tuberculosis	30 protein for 16 days	50-5-900	Faithful	Died pulmonary tuberculosis July 1921.	
452	F	Heb.	Housewife	50	Feb., '21	None	4	11	4	11	4	11	131	200	148	141	141	Hypertension. Sciatica	40 protein, 5 CH for 7 days	70-25-1200	Unreliable	Indifferent. Gave up treatment.	

453	M	Heb...	Merchant...	40	Feb., '21	Partial...	6	..	11	6	11	5	3	139	168	131	122	Pulmonary tuberculosis.	30 protein for 7 days	70-30-1800	Faithful...	Excellent fidelity and health.
454	F	Ger...	Housewife...	58	Feb., '21	Partial...	15	..	11	15	11	5	0	137	200	165	157	Cataracts. Carbuncles.	40 protein, 5 CH for 8 days	Unweighed.	Partial...	Lost from observation for 6 months. Glycosuria. Gaugrene developed. Returned for treatment. Abandoned treatment. Died June, 1921.
455	F	Heb...	Housewife...	47	Feb., '21	None...	9	..	11	9	11	5	7	155	223	149	148	Gall-stones.	30 protein for 4 days	65-15-1400	Faithful...	Returned for treatment. Abandoned treatment. Died June, 1921.
456	F	Heb...	Housewife...	22	Feb., '21	Restricted CH	0	4	4	0	8	5	4	126	137	112	109	None.	30 protein for 2 1/2 weeks	55-10-1200	Unfaithful.	Abandoned treatment. Died June, 1921.
457	F	Amer.	Housewife...	56	Feb., '21	Partial. Fair...	8	..	11	8	11	5	2	136	165	117	117	Hypertension. Hemiplegia.	40 protein, 5 CH for 6 days	75-30-1600	Faithful...	Follows diet. No glycosuria. Low blood sugars. Lost from observation.
458	M	Amer.	Merchant...	60	Feb., '21	Partial...	4	..	11	4	11	4	8	130	225	189	183	None.	40 protein, 5 CH for 4 days	80-30	Unfaithful.	Consultation case. Treatment was changed after operation. Good result. No glycosuria. Low blood sugar. No hyperglycemia. Excellent condition.
459	F	Heb...	Housewife...	49	Feb., '21	Partial...	6	..	11	6	11	5	3	139	Fibroid of uterus. Operation.	40 protein, 20 CH for 2 weeks	..	Faithful...	Consultation case. Treatment was changed after operation. Good result. No glycosuria. Low blood sugar.
461	M	Heb...	Merchant...	41	Feb., '21	Partial...	4	..	11	4	11	5	4	142	180	158	142	None.	1200 cal. for 4 days	Unweighed.	Faithful...	Good result. No glycosuria. Low blood sugar.
465	F	Heb...	School...	11	Feb., '21	None...	0	1	11	1	0	4	10	84	68	58	65	None.	50 protein, 10 CH and 800 cal. for 1 day	60-35-1700	Faithful...	No hyperglycemia. Excellent condition.
466	F	Heb...	Housewife...	40	Feb., '21	Free of glycosuria until 2 years ago	10	..	11	10	11	5	2	133	137	95	85	None.	30 protein for 2 weeks	60-20-1000	Faithful...	Tendency to hyperglycemia. No glycosuria.
467	M	Amer.	School...	20	Feb., '21	Controlled by total dietary restriction at intervals	2	..	6	2	6	5	6	139	115	78	76	Pulmonary tuberculosis.	20 protein for 5 days	45-5-1100	Faithful...	Abandoned treatment. Died Aug. 16, 1921.
468	M	Heb...	Merchant...	51	Feb., '21	None...	1	..	11	1	11	5	4	145	170	165	154	Neuritis. Hypertension.	1300 cal. for 1 week	Unweighed.	Faithful...	No glycosuria. Low blood sugar.
471	M	Heb...	Florist...	33	Feb., '21	Partial...	0	..	11	4	11	5	6	145	125	120	118	None.	1600 cal. for 2 weeks	Unweighed.	Faithful...	Good fidelity and health. Abandoned treatment. Died Nov., 1921, in coma.
474	M	Heb...	School...	12	Mar., '21	None...	4	2	8	0	10	5	0	83	88	66	65	Acidosis.	15 protein for 3 days	90-10-1200	Unfaithful.	Abandoned treatment. Died Nov., 1921, in coma.
475	M	Heb...	Merchant...	62	Mar., '21	Constant glycosuria past year	6	..	10	6	10	5	9	167	165	138	134	None.	Unweighed	Unweighed	Faithful...	Follows diet. No glycosuria.
476	M	Amer.	Teacher...	21	Mar., '21	None...	0	1	10	0	11	5	10	155	120	111	111	None.	30 protein for 4 days	65-25-1400	Faithful...	Follows diet. No glycosuria.
477	F	Amer.	Housewife...	54	Mar., '21	None. Disregarded diet	2	..	10	2	10	5	3	141	192	135	131	Hypertension. Neuritis.	40 protein, 5 CH for 2 weeks	70-20-1800	Faithful...	Follows diet. No glycosuria. Blood sugars low.
478	M	Heb...	Clerk...	29	Mar., '21	None...	0	6	4	0	10	5	8	150	195	196	201	Pulmonary tuberculosis.	Unweighed	Unweighed	Unfaithful	Careless. Alive. Not seen for 4 months.
480	M	Heb...	Cattleman...	47	Mar., '21	None...	3	..	9	1	0	5	8	161	220	181	175	None.	Unweighed	Unweighed	Partially faithful	No glycosuria for 3 months. Not seen since. Attempts to estimate sugar in diet. Fair result.
481	M	Heb...	Clerk...	23	Mar., '21	None...	0	6	10	1	4	5	6	139	155	135	128	None.	900 cal. for 1 day...	Unweighed	Faithful...	Good fidelity and health. No glycosuria. Blood sugars fairly low.
482	F	Amer.	Housewife...	44	Mar., '21	None...	2	..	10	2	10	5	8	155	170	138	129	Neuritis.	Unweighed	Unweighed	Faithful...	Good result. No glycosuria. Blood sugars fairly low.
486	F	Heb...	Housewife...	40	Mar., '21	Lax. Partial...	3	..	10	3	10	5	5	143	170	140	130	None.	Unweighed	Unweighed	Faithful...	Good result. No glycosuria. Blood sugars fairly low.
487	M	Heb...	Druggist...	35	Mar., '21	Partial. Restricted CH	5	..	10	5	10	5	11	172	185	149	139	None.	30 protein for 3 days	Unweighed	Faithful...	No glycosuria. Diet gradually reduced. Downward progress.
489	M	Italian	Child...	3	Mar., '21	Partial...	0	1	9	0	10	3	4	32	..	37	33	None.	40 protein, 10 CH for 1 day	80-30-1200	Faithful...	Mistakes in diet. Diet gradually reduced. Downward progress.
491	F	Heb...	Housewife...	50	Mar., '21	None...	4	..	10	4	10	5	5	148	178	152	147	Hypertension.	Unweighed	Unweighed	Partially faithful	No glycosuria. Improved. Faithful but ignorant.
492	M	Heb...	Hotelkeeper...	53	Mar., '21	Partial. Treated self	11	..	3	11	3	5	1	137	210	157	151	Hypertension. Arteriosclerosis.	30 protein for 10 days	Unweighed	Faithful...	Discontinued treatment. Died of gaugrene of scrotum, June, 1921.
495	F	Amer.	Housewife...	52	Mar., '21	Restricted CH. Intermittent glycosuria	3	..	10	3	10	5	4	144	210	169	167	Hypertension. Neuritis.	40 protein, 10 CH for 7 days	70-25-1600	Faithful...	Abandoned treatment. Downward progress. Alive.
496	F	Heb...	Housewife...	26	May, '21	None...	0	2	8	0	10	5	2	122	180	146	121	Neuritis.	30 protein for 3 months	50-5-1000	Partial	Changed treatment. Living.
497	F	Amer.	Housewife...	34	Mar., '21	Partial. Constant glycosuria recently	2	..	10	2	10	5	2	125	125	109	92	None.	30 protein for 3 weeks	40-5-700	Faithful...	Increased diet. Downward progress. Abandoned treatment.
499	F	Amer.	Housewife...	51	Mar., '21	Partial. Admitted without glycosuria	1	..	9	1	9	5	3	141	123	59	57	None.	30 protein for 1 week	40-5-800	Faithful...	Severe case. Died Dec. 3, 1921.

TABLE IV (Continued)

Case No.	Sex	Race	Occupation	Age at admission	Date of Admission	Treatment Before Admission	DURATION OF DIABETES				HEIGHT		BODY WEIGHT				Complications	Initial Treatment	Final Diet, Protein, CH and Total Cal.	Degree of Fidelity	Result	
							Before Admission		Total	HEIGHT		Pounds	Standard Normal	Before Admission	Final							
							Yr.	Mo.		Ft.	In.											
																Yr.						Mo.
503	F	Amer.	Housewife	40	Feb., '21	Poor. Glycosuria most of time	2	11	2	11	5	6	147	200	131	121	Abdominal adhesions	30 protein for 3 weeks	350-5-800	Faithful	Carless. Return of glycosuria. Living.	
504	M	Amer.	Mfr.	55	Feb., '21	Intermittent glycosuria	4	11	4	11	5	8	162	200	168	152	Hypertension	40 protein, 5 CH for 18 days	85-40-2200	Faithful	Weighs diet. Blood sugars low. No glycosuria. Good result.	
505	F	Heb.	Housewife	34	Feb., '21	None	0	3	11	1	2	5	4	132	195	150	150	Pregnancy	50 protein, 10 CH for 2 days	70-30-2000	Faithful	No glycosuria. Blood sugars low. Gave birth to normal child.
509	M	Amer.	Clerk	51	Mar., '21	None	8	6	8	6	5	4	145	184	108	100	Cirrhosis of liver. Fibrous myocarditis	30 protein for 35 days	19-55-20-1600	Faithful	Carless with diet. Died of cirrhosis Sept., 1921.	
510	M	Amer.	College	18	Jan., '21	Restricted sugar	0	6	12	1	6	5	7	136	150	139	130	None	35 protein, 10 CH, 400 cal. for 10 days	Unweighed	Faithful	Good health. Mild case.
511	M	Amer.	Clerk	61	Jan., '21	None	2	12	1	2	5	9	167	250	137	125	Atelectasis of lung. Tubercular pharyngitis	20 protein for 20 days	10-50-10-800	Broke diet	Abandoned treatment	
514	F	Amer.	School	14	Apr., '21	Partial	1	7	4	1	11	5	2	104	96	62	63	None	30 protein for 30 days	16-40-10-700	Faithful	Died of inanition August, 1921.
515	F	Amer.	Nurse	60	Apr., '21	Restricted sugar and starch	8	9	8	9	5	3	141	194	120	102	Hypertension	50 protein, 10 CH, 1000 cal. for 1 week	65-15-1800	Faithful	Good fidelity and health.	
516	M	Amer.	Clerk	48	Apr., '21	Partial	3	9	1	0	5	6	152	200	177	168	Cirrhosis of liver	40 protein, 5 CH for 7 days	65-20-1700	Faithful	Abandoned treatment.	
518	M	Amer.	Child	3	Apr., '21	None	0	1	0	10	3	4 1/2	33	42	40	36	Acidosis	30 CH for 1 day	65-30-1450	Faithful	Breaks diet occasionally. Healthy.	
519	M	Heb.	Auctioneer	40	Apr., '21	None	1	9	0	10	5	9	164	162	135	132	None	30 protein for 4 days	Unweighed	Unfaithful	Abandoned treatment.	
520	M	Amer.	R.R. official	64	Apr., '21	Partial	6	9	6	9	5	11	178	237	201	200	None	60 protein, 15 CH for 2 days	Unweighed	Faithful	Follows diet. Good result.	
524	F	Amer.	Hotelkeeper	60	Mar., '21	None	1	10	1	10	5	2	138	246	215	204	None	40 protein, 5 CH for 6 days	Unweighed	Faithful	Follows diet partially.	
525	F	Heb.	Housewife	57	Apr., '21	Partial	10	9	10	9	5	0	133	175	122	119	Hypertension	35 protein, 5 CH for 6 days	65-10-1200	Faithful	Good. Slight hyperglycemia.	
526	M	Amer.	Banker	48	Mar., '21	Lax	5	10	5	10	5	9	166	177	135	127	None	30 protein for 10 days	55-10-1200	Faithful	Treats self. Glycosuria.	
528	F	Ger.	Housewife	54	Apr., '21	Partial	12	9	12	9	5	0	133	140	119	98	Cataracts	30 protein for 3 days	Unweighed	Faithful	Good.	
529	F	Amer.	Child	10	Mar., '21	None	1	4	10	2	2	4	0 1/2	52	56	54	51	None	20 protein, 5 CH for 2 days	50-10-1000	Faithful	Excellent condition. Normal blood sugar on weighed diet. Height 5 ft. 1 1/2 inches Jan. 1, 1922.
530	M	Heb.	Merchant	42	Mar., '21	Partial	0	5	10	1	3	5	8	159	164	155	152	Hypertension	Unweighed	Unweighed	Partial	Lost from observation.
531	F	Amer.	Nurse	51	Mar., '21	Restricted CH	0	5	10	1	3	5	4	144	170	118	86	Hypertension. Acidosis	35 protein for 35 weeks	55-15-1500	Faithful	Carless with diet. Glycosuria. Returned for further treatment.
532	F	Amer.	School	24	Mar., '21	Glycosuria absent first year, now constant	2	10	2	10	4	11	113	194	91	76	None	20 protein for 20 days	12-50-10-1200	Faithful	Good.	
534	M	Amer.	School	14	Feb., '21	None	0	2	11	1	1	5	3	107	110	96	126	None	500 cal. for 1 day	90-45-2200	Faithful	Occasional hyperglycemia. Weighs diet. Growing. In school.
535	M	Heb.	Furrier	44	Mar., '21	None	3	10	3	10	5	4	142	142	102	90	None	30 protein for 3 weeks, with 7 fast days	45-50-1100	Unfaithful	Patient increased diet. Careless. Downward progress.	
536	F	Heb.	Housewife	42	Apr., '21	None	0	2	9	0	11	5	5	143	197	115	132	Hypertension	30 protein for 1 week	70-25-1800	Faithful	Good. Normal blood sugar.

539	F Amer.	School	7 May, '21	0	5	8	1	1	4	0½	52	43	38	45	Acidosis.	25 protein for 2 days	50-15-1100.	Faithful...	No hyperglycemia. Goes to school.
540	F Amer.	School	11 May, '21	1	..	4	1	4	4	6	68	55	46	35	Acidosis.	10 protein for 4 days	40-25-600.	Faithful...	Abandoned treatment. Died Sept., 1921.
541	F Amer.	School	8 May, '21	0	6	8	1	2	3	11½	49	49	33	455	None.	10 protein for 2 days	40-10-900.	Unfaithful.	Incorrigible breaking of diet. Glycosuria at irregular intervals.
542	M Amer.	Business	46 May, '21	9	..	2	9	2	6	0	183	250	143	139	Pulmonary tuberculosis.	30 protein with fast, 30 days for 1 month	30-1-400.	Faithful...	Died of tuberculosis July, 1921.
543	M Dan.	School	11 May, '21	0	1	4	10	78	90	76	76	None.	30 protein for 7 days	50-15-1200.	Faithful...	Occasional hyperglycemia. In school.
544	M Amer.	Clerk	34 May, '21	0	2	10	5	4	137	155	118	117	None.	20 protein for 8 days	50-10-1000.	Faithful...	Good.
546	F Amer.	Stewardess	30 May, '21	2	6	8	3	2	5	6	140	124	78	68	None.	Complete fast for 11 days. Then alternating fast and 400 cal. for 20 days	40-5-800.	Faithful...	Abandoned treatment.
553	F Amer.	School	14 May, '21	5	..	6	6	6	4	6	70	72	51	51	None.	20 protein for 18	30-1-350.	Faithful...	Very severe diabetes. Abandoned treatment. Dead.
558	F Heb.	Housewife	52 May, '21	12	..	8	12	8	5	3	141	180	143	138	Hypertension.	30 protein for 7 days	85-20-1500.	Unfaithful.	Glycosuria occasionally. Fair result
573	F Heb.	Housewife	33 May, '21	0	5	8	1	1	5	3	128	135	103	93	None.	30 protein for 12	40-5-..	Unfaithful.	Broke diet while under treatment. Discharged. Died Dec., 1921.
574	F Heb.	Child	2 May, '21	0	2	8	..	10	2	10½	35	30	18	22	None.	15 protein, 10 CH for 5 days	35-10-800.	Faithful...	Good. Normal blood sugars.
578	F Amer.	School	10 Apr., '21	0	6	9	1	3	4	6	69	70	55	61	Acidosis.	20 protein, 40 CH for 5 days	65-40-1600.	Partially faithful	Occasional breaks of diet. Good condition on weighted diet
581	M Heb.	Merchant	60 Apr., '21	0	1	9	..	10	5	6	153	165	133	133	Neuritis.	40 protein, 5 CH for 3 days	75-25-1900.	Faithful...	Good.
584	F Amer.	Housewife	39 Apr., '21	1	..	3	1	3	5	2	125	155	120	114	None.	30 protein for 3 days	85-20-1500.	Faithful...	Followed treatment well for 3 months. No report since.
587	F Amer.	School	16 Apr., '21	0	4	9	1	1	5	6	130	152	114	95	None.	30 protein for 6 days	80-25-1600.	Faithful...	No hyperglycemia. Good health.
588	F Heb.	Housewife	50 Apr., '21	3	9	9	3	9	5	6	152	210	174	161	Gall-stones. Hypertension.	30 protein for 10	70-20-1000.	Faithful...	Follows diet. Not seen recently.
591	F Heb.	Housewife	44 Aug., '21	5	..	9	5	9	4	11	126	152	97	90	None.	30 protein, 10 CH for 2 weeks	55-5-1100.	Faithful...	Treating self. Sugar-free.
593	M Amer.	Lawyer	58 Apr., '21	1	..	9	1	9	5	9	167	179	168	168	None.	1500 cal. for 1 day.	85-45-1900.	Faithful...	Good.
596	F Ger.	Housewife	46 May, '21	2	..	8	2	8	5	9	163	225	200	146	None.	Unweighed.	Unweighed.	Faithful...	Excellent. Normal blood sugar.
597	F Heb.	Housewife	63 May, '21	20	..	8	20	8	5	1	135	200	145	135	Hypertension.	30 protein, 5 CH for 8 days	70-10-1800.	Faithful...	Follows diet. Makes mistakes.
598	F Heb.	Book-keeper.	39 June, '21	11	..	7	11	7	4	11	122	130	130	124	None.	800 cal. for 1 day.	75-30-1700.	Faithful...	Good result, on unweighed diet.
601	M Amer.	Lumberman.	68 May, '21	10	..	8	10	8	5	1	137	175	151	151	Neuritis.	1000 cal. for 1 day.	Unweighed.	Faithful...	Good. Followed diet few months. Became careless.
602	M Heb.	Business	45 May, '21	6	..	8	6	8	5	5	161	205	185	178	Neuritis.	30 protein, 5 CH for 2 days	80-30-..	Unfaithful.	Followed diet few months. Became careless.
603	F Amer.	School	44 May, '21	1	5	8	2	1	3	10½	47	40	37	38	Acidosis.	40 CH for 2 days	40-20-700.	Faithful...	Abandoned treatment.
610	M Amer.	Surgeon	7 May, '21	1	..	8	1	8	6	1	157	217	152	133	Neuritis.	40 CH for 3 days	70-20-1900.	Faithful...	Excellent. Normal blood sugar.
611	M Heb.	Druggist	61 May, '21	11	..	3	11	8	5	1	137	145	106	101	Gangrene. Retinitis. Calculi.	30 protein for 4 days	70-30-1500.	Faithful...	Lost from observation.
612	F Amer.	Housewife	59 May, '21	12	..	8	12	8	137	124	118	118	Neuritis.	30 protein, 5 CH for 3 weeks	80-10-600.	Faithful...	Abandoned treatment immediately.
613	M Heb.	Insurance	49 May, '21	4	..	8	4	8	5	11	177	202	171	161	None.	40 protein, 10 CH for 6 days	70-20-1800.	Faithful...	Excellent. Normal blood sugar.
616	M Amer.	Child	1½ May, '21	1 wk.	..	8	0	8	2	6½	..	22	18	18	Acidosis.	15 protein, 15 CH for 3 days	85-40-750.	Faithful...	No hyperglycemia. Good condition
617	M Amer.	Business	39 June, '21	0	1	7	0	8	5	11	172	20	168	162	None.	1000 cal. for 1 day.	85-50-2200.	Faithful...	Excellent. Normal blood sugar on unweighed diet.
618	M Heb.	Laborer	34 June, '21	0	6	7	1	1	5	10	163	138	125	119	None.	Unweighed.	Unweighed.	Faithful...	Normal blood sugar on unweighed diet.
620	M Amer.	Salesman	50 June, '21	3	..	7	3	7	5	6	153	220	133	120	Gangrene. Leg amputated June 26, 1921	25 protein, 5 CH for 7 days	50-10-800.	Faithful...	Died Jan. 6, 1922, of pulmonary embolism.
621	M Amer.	Contractor	55 June, '21	8	..	7	8	7	6	2	198	255	208	190	Neuritis.	40 protein, 10 CH for 4 days	85-40-2000.	Faithful...	Good.
624	F Heb.	Housewife	52 June, '21	3	..	7	3	7	5	0	133	171	131	114	Hypertension.	30 protein for 4 days	75-20-1000.	Faithful...	Good.

TABLE IV (Continued)

Case No.	Sex	Race	Occupation	Age at Admission	Date of Admission	Treatment Before Admission	DURATION OF DIABETES				HEIGHT	BODY WEIGHT				Complications	Initial Treatment	Final Diet, Protein, CH and Total Cal.	Degree of Fidelity	Result	
							Before Admission		Total	Pounds											
							Yr.	Mo.		Standard Normal		Before Admission	Final								
														Ft. In.	...						
629	M	Feb.	Business	37	June, '21	Disregarded diet.	7	6	7	6	5	10	167	220	140	108	Pending coma.	30 protein and 40 CH for 1 week	Unweighed.	Unfaithful	Seen once. Acidosis cleared. Died 6 months later.
630	F	Feb.	Housewife	46	Oct., '21	Practically none.	5	3	5	3			155	124	108		25 protein for 9 days	50-5-800	Faithful	Still under treatment.	
631	F	Feb.	Housewife	40	June, '21	Restricted CH.	2	7	2	7	5	4	139	180	169	164	None.	Unweighed.	Unweighed.	Faithful	Severe diabetes.
632	M	Mar.	Farmer	27	June, '21	Tested for glycosuria recently	2	7	2	7	5	3	131	150	120	108	None.	30 protein for 9 days	65-20-1600	Faithful	Good. Fair result.
635	M	Mar.	Insurance	57	June, '21	Partial. Sugar most of time	7	7	7	7	6	0 1/4	184	250	213	205	None.	40 protein, 10 CH for 3 days	90-55-2000	Faithful	Good.
638	M	Mar.	Carpenter	55	July, '21	Partial.	1	6	1	6	5	10	172	290	200	190	Furuncles.	30 protein for 2 days	Unweighed.	Faithful	Good. Works as carpenter.
639	F	Feb.	Housewife	32	July, '21	Sugar constantly.	0	5	0	5	2	125	150	135	117	Pruritus.	Unweighed.	Unweighed.	Faithful	Never glycosuria. Tendency to hypoglycemia.	
641	M	Feb.	Business	48	July, '21	Sugar most of time	1	6	2	0	5	4	144	173	159	149	Hypertension. Carbuncle	30 protein, 5 CH for 2 days	85-30-1800	Faithful	Good. Low blood sugar.
642	M	Mar.	Business	32	June, '21	None; indifferent	1	6	5	1	5	10	163	297	134	141	None.	30 protein for 4 weeks	40-5-1000	Faithful	Abandoned treatment. Died Nov., 1921.
645	F	Mar.	Housewife	45	July, '21	Sugar constantly.	5	6	6	6	5	2	136	165	128	118	Hypertension. Acidosis.	10 protein for 2 weeks	40-5-500	Faithful	Abandoned treatment.
646	F	Feb.	Housewife	47	July, '21	None	5	6	5	6	5	3	139	225	174	160	Hypertension. Melancholia	40 protein for 7 days	60-20	Faithful	Makes mistakes. Good condition.
647	F	Feb.	Housewife	55	July, '21	None	2	6	2	6	5	0	133	140	90	100	Hypertension. Hyperthyroidism. Myocarditis	30 protein for 2 weeks	30-15-1100	Faithful	Good.
648	M	Mar.	Business	46	July, '21	Fair. Sugar-free until past year	6	6	6	6	5	7	155	165	115	105	None.	10 protein for 2 weeks	50-5-1000	Unfaithful	Good. Follows diet.
649	F	Feb.	Housewife	54	July, '21	Partial.	1 wk.	6	0	7	5	3	141	215	153	140	None.	30 protein, 5 CH for 11 days	70-15-1600	Faithful	Makes mistakes. Fair result.
653	M	Mar.	Farmer	36	July, '21	Increased food to gain weight; lost	1	5	1	5	5	6	143	145	99	91	None.	20 protein for 2 weeks	40-5-900	Faithful	Treating self. Sugar-free.
654	F	Mar.	Housewife	57	July, '21	Partial.	4	6	4	6	5	1	135	165	98	85	Hypertension. Myocarditis	20 protein for 5 weeks	40-5-700	Faithful	Abandoned treatment.
656	F	Feb.	Housewife	47	July, '21	Partial.	5	6	5	6	5	2	136	210	149	130	None.	30 protein for 4 weeks	45-5-600	Faithful	Gave up treatment.
659	M	Mar.	School	13	July, '21	No glycosuria.	1	6	1	7	4	8	78	72	72	71	None.	35 protein, 5 CH for 2 days	55-20-1100	Faithful	Good. In school.
662	F	Mar.	Housewife	60	July, '21	None.	0	4	6	0	10	5	144	164	139	130	Hypertension.	45 protein, 5 CH and 900 cal. for 7 days	Unweighed.	Faithful	Good. Normal blood sugar.
667	F	Feb.	Housewife	70	July, '21	None.	2	6	2	6	4	11	131	172	120	112	Sciatica. Arteriosclerosis	35 protein, 5 CH for 10 days	60-10-1200	Faithful	Abandoned treatment.
668	M	Feb.	Merchant	60	July, '21	None.	8	6	8	6	5	9	167	169	135	137	Hypertension.	30 protein for 9 days	65-15-1500	Faithful	Changed treatment.
670	M	Feb.	Furrier	62	July, '21	Partial	1	6	1	6	5	6	153	210	101	146	Hypertension.	90 protein, 20 CH and 800 cal. for 7 days	30-25-1500	Faithful	Not seen since discharge.
672	M	Mar.	Business	37	Nov., '21	None.	0	6	2	0	8					Boils.	Low unweighed diet.	Unweighed.	Faithful	Boils disappeared. Low blood sugar.	

673	M	Amer.	Lawyer	64	Aug.	'21	None	2	5	2	5	5	8	102	185	147	155	Cataract	40 protein, 10 CH for 3 days	75-25-1700.	Faithful	Good.	
675	F	Heb.	Housewife	54	Aug.	'21	Partial	3	5	3	5	5	0	133	145	115	104	None	30 protein for 4 days	80-30-1800.	Faithful	Good. No hyperglycemia.	
676	M	Heb.	Clerk	29	Aug.	'21	None	2	5	2	5	5	7	146	105	113	97	Hyperthyroidism	30 protein for 3	40-5-800.	Faithful	Good. Changed treatment.	
677	F	Heb.	Housewife	46	July,	'21	Partial	8	6	8	6	5	1	133	200	144	132	None	35 protein, 5 CH for 7 days	70-15-800.	Faithful	Good.	
679	F	Heb.	Housewife	48	Aug.	'21	Lax	7	5	7	5	5	4	132	150	129	121	None	Unweighed	Unweighed.	Faithful	Good.	
680	F	Amer.	Nurse	30	Aug.	'21	Glycosuria absent 9 months; now difficult to control	1	5	1	5	5	4	132	143	115	81	None	15 to 30 protein and numerous fast-days for 3 months	50-20-1200.	Faithful	Good. Uncontrollable case.	
683	M	Heb.	Housewife	56	Aug.	'21	Constant glycosuria	0	5	1	1	5	3	141	152	100	99	None	30 protein for 3 weeks	340-5.	Faithful	Abandoned treatment.	
686	F	Heb.	Housewife	50	Aug.	'21		3	5	3	5	4	7	123	158	129	120	Hypertension	35 protein, 5 CH for 8 days	60-15.	Faithful	Weighted diet. Good result.	
687	F	Irish.	Nun	61	Aug.	'21	Almost constant glycosuria	12	5	12	5	5	7	157	180	110	102	None	40 protein, 5 CH for 2 weeks	50-5-000.	Faithful	Severe case. Makes mistakes.	
688	F	Heb.	Housewife	48	Aug.	'21	None	4	5	4	5	4	11	129	225	102	151	Neuritis	30 protein for 5 days	50-50.	Faithful	Good.	
689	M	Heb.	Merchant	43	Aug.	'21	Partial	3	5	3	5	5	5	146	152	143	136	None	30 protein for 4 days	85-45-2000.	Faithful	Good. Normal blood sugar.	
692	M	Amer.	Engineer	62	Sept.	'21	Partial	3	4	3	4	5	7	157	175	132	136	None	Unweighed	Unweighed.	Faithful	Good. Blood sugar low.	
693	F	Heb.	Housewife	65	Aug.	'21	Good. Glycosuria rarely	1	5	1	5	5	10	129	126	99	96	None	30 protein for 7 days	65-15-1600.	Faithful	Good. Blood sugar low.	
694	F	Heb.	Housewife	41	Sept.	'21	None	2	4	2	4	5	1	130	155	129	123	Salivaria	30 protein for 4 days	50-10-1500.	Faithful	Lost from observation.	
698	M	Amer.	Real estate	60	Sept.	'21	Free of glycosuria	0	3	1	1	5	7	157	200	154	143	None	30 protein, 5 CH for 6 days	Unweighed.	Faithful	Good. No hyperglycemia.	
700	F	Amer.	Housewife	71	Aug.	'21	Partial	3	5	3	5	5	2	138	163	132	127	None	30 protein for 4 days	75-45-1900.	Faithful	Good. Normal blood sugar.	
708	M	Amer.	School	11	May,	'21	Free of glycosuria	2	6	3	2	3	8 ³ / ₄	77	82	75	76	None	35 protein, 5 CH for 9 days	60-30-1500.	Faithful	Good. In school.	
709	F	Amer.	Clerk	17	May,	'21	No glycosuria	1	8	1	8	5	4	123	120	112	111	None	30 protein for 7 days	Unweighed.	Unfaithful	Discharged.	
711	F	Amer.	Housewife	55	June,	'21	None	0	2	7	0	9	3 ³ / ₄	141	170	124	121	Neuritis	30 protein for 6 days	Unweighed.	Faithful	Good.	
712	M	Heb.	Merchant	63	June,	'21	Glycosuria most of time	15	7	1	10	5	2	139	165	135	132	Hypertension. Edema	40 protein, 10 CH for 7 days	Unweighed.	Faithful	Changed treatment.	
718	F	Amer.	Housewife	51	June,	'21	Restricted sugar and starch	12	7	1	7	5	6	152	180	136	131	None	40 protein, 10 CH for 8 days	45-5-700.	Faithful	Abandoned treatment.	
719	F	Italian	Housewife	38	June,	'21	Partial	1	7	1	7	5	4	136	230	210	133	Boils	40 protein, 10 CH for 8 days	90-60-1700.	Faithful	Good. No hyperglycemia.	
720	M	Amer.	Housewife	33	June,	'21	None	0	1	7	0	8	5	3	134	150	121	116	None	30 protein for 2 days	Unweighed.	Faithful	Excellent. No hyperglycemia.
723	F	Irish.	Housewife	49	June,	'21	None. Constant glycosuria	1	7	1	7	4	11	129	176	131	128	Hypertension	30 protein for 7 days	Unweighed.	Faithful	Ignorant. No glycosuria.	
724	M	Amer.	Supt.	70	June,	'21	Partial	2	2	2	2	5	9	137	160	107	91	None	30 protein for 3 weeks	350-5-1100.	Faithful	Abandoned treatment. Died Aug. 11, 1921.	
725	M	Amer.	Secretary	45	June,	'21	None until 8 months ago	8	6	6	5	10	171	135	103	84	84	Pulmonary tuberculosis	30 protein for 5 weeks	55-15-1400.	Faithful	Abandoned treatment. Died Dec. 1921.	
731	M	Amer.	Clerk	29	June,	'21	None	1	7	1	7	5	7	146	132	104	89	None	20 protein for 5 weeks	60-10-1200.	Faithful	No report since discharge.	
734	F	Heb.	Housewife	55	June,	'21	Glycosuria most of time	8	7	8	7	4	10	129	145	84	83	None	30 protein for 2 weeks	40-5-600.	Unfaithful	No report since discharge.	
739	F	Amer.	Housewife	30	June,	'21	None	0	1	7	0	8	5	3	128	130	107	104	None	30 protein for 1 week	100-10-900.	Faithful	Changed treatment.
743	M	Amer.	Farmer	47	June,	'21	Sugar-free until past 6 months	3	7	3	7	5	11	177	172	125	111	None	40 protein, 5 CH for 6 days	60-20-1500.	Faithful	Good.	
745	M	Heb.	Housewife	48	June,	'21	Intermittent glycosuria	3	7	3	7	5	1	136	164	133	131	Hypertension	40 protein, 10 CH for 4 days	75-25-1700.	Faithful	Good.	
746	M	Heb.	Musician	51	June,	'21	None	4	7	0	11	210	...	100	100	Retinitis. Cystitis	30 protein for 5 days	40-5-800.	Faithful	Abandoned treatment. Mistakes. Glycosuria. Downward progress.	
747	M	Heb.	Child	4	June,	'21	No glycosuria	0	7	7	1	2	3	1	...	29	28	None	30 protein for 2 days	50-15-900.	Faithful	Excellent. Never hyperglycemia.	
749	M	Amer.	School	10	June,	'2	Partial	0	2	7	0	9	4	80	90	90	79	None	30 protein for 10 days	55-20-1400.	Faithful	Excellent. Never hyperglycemia.	

TABLE IV (Continued)

Case No.	Sex	Race	Occupation	Age at Admission	Date of Admission	Treatment Before Admission	DURATION OF DIABETES				HEIGHT		BODY WEIGHT				Complications	Initial Treatment	Final Diet, Protein, CH and Total Cal.	Degree of Fidelity	Result	
							Before Admission		After Admission		Ft.	In.	Pounds									
							Yr.	Mo.	Yr.	Mo.			Standard	Before Admission	At Dismission							
																Total						Yr.
752	F	Heb.	Housewife	55	June, '21	No glycosuria first 6 years. Then ate everything	7		7	7	4	10	129	148	68	68	None.	15 protein for 1 month	150-5-1100.	Faithful.	Severe case. Broke diet immediately upon discharge. Living.	
753	M	Irish	Chauffeur	35	June, '21	None.	2		1	2	1	6	0	178	180	131	120	Pancreatic calculi?	20 protein for 12 days	12 40-5-800.	Faithful.	Died July 13, 1921.
754	F	Amer.	Housewife	58	July, '21	Partial	8		6	8	6	5	6	152	207	152	131	Hypertension. Retinitis.	30 protein for 5 days	65-20-1000.	Faithful.	Follows diet. Fair result.
757	F	Amer.	Housewife	70	July, '21	Restricted CH	2		7	2	7	5	6	152	170	147	143	None.	30 protein for 1 day	35-40-2000	Faithful.	Good. Low blood sugars.
758	F	Heb.	Housewife	58	July, '21	Practically none.	6		7	6	7	5	1	135	170	131	126	Boils.	30 protein for 6 days	75-15-1400	Faithful.	Good.
759	F	Amer.	School	17	July, '21	None.	1	6	7	2	1	5	4	123	108	104	97	Acidosis.	30 protein for 4 days	55-15-1400.	Faithful.	Tendency to hyperglycemia.
761	F	Irish	Housewife	57	July, '21	None.	2	weeks	7	0	7	5	5	145	202	177	167	Boils.	30 protein for 6 days	70-20-1600	Faithful.	No glycosuria.
763	M	Heb.	Merchant.	50	July, '21	Partial	0	6	7	1	1	5	3	142	155	134	150	Neuritis.	40 protein, 5 CH for 3 days	70-30-1800.	Faithful.	Good. Low blood sugar. Lost from observation.
764	M	Amer.	Mechanic.	18	May, '21	None.	2		8	2	8	5	6	132	190	132	101	None.	15 protein with alternate fast-days for 7 weeks	30-10-1000.	Faithful.	Careless with diet. Sugar-free.
766	M	Amer.	Business	37	Aug., '21	Poor.	4		2	4	2	5	6	148	156	99	83	None.	30 protein for 16 days	50-5-900.	Faithful.	Died Oct. 17, 1921.
767	M	Heb.	Insurance.	70	May, '21	Laax. Restrictd CH	6		8	6	8	5	4	145	187	106	92	None.	30 protein for 12 days	70-30-2100.	Faithful.	Excellent. Low blood sugar.
768	M	Heb.	School	8	July, '21	None.	0	6	6	1	0	4	5	63	64	53	51	None.	30 protein for 13 days	45-10-900.	Faithful.	Good. Tendency to hyperglycemia.
770	M	Ger.	Business	71	July, '21	None.	0	1	7	0	8			186	142	136	120	Pulmonary tuberculosis.	40 protein for 18 days	80-40-1700.	Faithful.	Lost from observation.
771	M	Heb.	Rabbi.	55	July, '21	No bread or sugar eaten	18		7	13	7	5	5	149	160	121	120	None.	30 protein for 10 days	Unweighed.	Faithful.	Treating self. Sugar-free.
773	M	Heb.	Polreman	43	July, '21	None.	0	2	7	0	9	5	6	150	219	162	152	None.	30 protein for 1 day	Unweighed.	Faithful.	Fair. Hyperglycemia.
774	M	Ger.	Postal clerk.	36	July, '21	Careless. Constant glycosuria	5	0	7	5	7	5	9	162	148	117	118	None.	30 protein for 7 days	65-15-1400.	Broke diet.	Abandoned treatment.
776	M	Amer.	Lawyer	64	July, '21	Glycosuria 20 yrs. ate no sugar	20		7	20	7	5	10	172	225	192	184	None.	40 protein, 10 CH for 2 days	30-25-1600	Faithful.	Good. Improved health.
780	M	Amer.	College.	18	July, '21	Partial.	1		7	1	7	5	11	153	188	148	148	None.	40 protein, 5 CH for 4 days	50-10-1400.	Broke diet.	Discharged for breaking diet.
783	F	Amer.	School	22	July, '21	Good. Blood sugar kept low	9		7	9	7	5	5	123	133	87	82	None.	30 protein for 7 days	55-15-1000.	Faithful.	Normal blood sugar. Finished college.
784	M	Heb.	Business	45	Sept., '21	None.	0	6	4	0	10	5	3	141				None.	30 protein for 6 days	75-35-1800.	Faithful.	Good.
785	M	Heb.	Restaurant-keeper	42	July, '21	Disregarded diet.	9		7			5	8	159	220	190	184	Neuritis.	35 protein, 10 CH for 1 day	85-40-1600.	Broke diet.	Abandoned treatment.
786	M	Amer.	School	11	July, '21	Partial.	2		3	2	3	4	2 $\frac{3}{4}$	61	60	49	46	Acidosis.	20 protein for 18 days	40-10-600.	Broke diet.	Broke diet. Died Oct., 1921.
787	M	Amer.	Merchant.	43	July, '21	Partial.	1		6	1	6	6	0	181	229	179	147	None.	40 protein, 10 CH for 3 weeks	75-20-1600.	Faithful.	Good.
788	M	Amer.	Clerk	39	July, '21		7		7	7	7							None.	40 protein, 10 CH for 7 days	80-25-1300.	Faithful.	Careless. Gave up treatment.
789	M	Heb.	Tailor.	57	Aug., '21	None.	0	8	6	1	0	5	6	153	178	134	127	Pulmonary tuberculosis.	30 protein for 3 weeks	340-5-800.	Faithful.	Gave up treatment. Alive.
790	F	Heb.	Housewife	39	Aug., '21	None.	0	1	5	0	6	5	0	124	130	72	68	Asthma.	30 protein for 3 days	65-20-1700.	Faithful.	Good. Normal blood sugar.

793	M Heb.	Merchant...	56	Sept., '21	Partial.	12	..	4	12	4	6	0	184	160	99	90	None.	20 protein for 5 weeks	5 60-10-1200.	Faithful.	Follows diet.	Fair result.	
795	M Heb.	Clerk.	27	Sept., '21	None.	0	5	4	0	9	6	2	181	142	109	95	Boils.	15 protein for 3 weeks	3 60-15-1400.	Faithful.	Good.	Normal blood sugar.	
800	F Amer.	Housewife...	35	Aug., '21	Fair.	1	5	4	0	9	5	5	142	144	92	86	None.	30 protein for 4 days	55-10-900.	Faithful.	Fair.	Changed doctors.	
801	M Irish.	Garagekeeper	49	Aug., '21	Intermittent glycosuria.	0	5	4	0	9	5	6	148	144	92	86	Pancreatic calculi?	30 protein for 5 days	60-15-1200.	Faithful.	Dec., 1921.	Died of infection.	
805	M Heb.	Butcher.	33	Aug., '21	None.	0	8	5	1	1	5	43	137	195	159	148	None.	40 protein for 5 days	85-40-2000.	Faithful.	Good.	Normal blood sugar.	
806	F Amer.	Child.	7	Aug., '21	None.	0	4	5	0	9	4	0	52	50	40	37	Acidosis.	50 CH for 5 days.	55-15-850.	Faithful.	Good.	Normal blood sugar.	
807	M Heb.	Merchant.	44	Aug., '21	None.	7	5	5	7	5	5	3	139	221	161	166	None.	40 protein, 5 CH for 3 days.	Unweighed.	Faithful.	Good.	Normal blood sugar.	
811	F Heb.	Housewife...	50	Aug., '21	Partial at first. Glycosuria past 6 years	13	..	5	13	5	5	4	144	275	157	151	Hypertension.	Carbun- cles	40 protein, 5 CH for 6 days.	60-15-1400.	Faithful.	Good.	
812	F Heb.	Housewife...	49	Aug., '21	Partial. Lax.	13	..	5	13	5	5	4	142	200	169	161	Hypertension.	40 protein, 5 CH for 5 days	70-20-1650.	Faithful.	Good.		
813	M Amer.	Physician...	32	Aug., '21	Sugar-free most of time	8	..	5	8	5	6	1	180	..	126	121	None.	30 protein for 3 weeks	3 50-10-1100.	Faithful.	Good.		
815	F Heb.	Housewife...	49	Aug., '21	Constant glycosuria	0	7	5	1	0	5	1	133	168	118	111	Boils.	40 protein, 10 CH for 4 days	65-10-1100.	Faithful.	Fair.	Careless.	
816	F Heb.	Home...	46	Aug., '21	Lax. Glycosuria most of time	2	..	5	2	5	5	1	133	132	109	108	None.	40 protein, 5 CH for 2 weeks	70-30-1600.	Faithful.	Good.		
818	F Amer.	Housewife...	45	Aug., '21	No glycosuria first year. Careless since	4	..	5	4	5	5	3	139	185	109	100	Gall-stones.	20 protein for 3 days	40-5-900.	Unfaithful.	Abandoned diet.		
820	M Heb.	Business...	38	Aug., '21	None.	0	1	5	0	6	5	9	162	147	136	129	None.	40 protein, 5 CH for 4 days	65-10-1100.	Faithful.	Changed doctors.		
823	M Amer.	Merchant...	25	Aug., '21	None.	0	10	5	1	3	5	7	146	122	89	90	Acidosis.	25 protein for 11 days	70-30-1700.	Faithful.	Lax in diet.	Fair result.	
824	F Heb.	Housewife...	49	Aug., '21	Partial. Intermittent glycosuria	13	..	5	13	5	4	10	127	118	104	88	None.	25 protein for 25 weeks	65-15-1200.	Faithful.	Good.	Normal blood sugar.	
826	F Amer.	School...	15	Aug., '21	None.	1	..	5	1	5	5	4	123	128	93	88	None.	30 protein for 10 days. Alternate fast-days with 30 protein for 10 days	50-10-1000.	Faithful.	Follows diet.	No report recently.	
827	M Amer.	Automobile agent	65	Aug., '21	None.	8	..	5	8	5	5	8	162	227	178	164	Carbuncles.	40 protein, 5 CH for 2 weeks	70-25-1800.	Faithful.	Free from glycosuria.		
828	M Amer.	Professor.	44	Aug., '21	None.	0	1	5	0	6	5	8	159	140	110	119	None.	10 protein, 5 CH for 1 day	70-25-1400.	Faithful.	Changed doctors.		
830	F Heb.	Housewife...	50	Sept., '21	Partial.	1	..	4	1	4	5	0	133	170	140	132	None.	30 protein for 6 days	30-5.	Faithful.	Abandoned treatment.		
831	F Amer.	Housewife...	39	Sept., '21	Partial.	1	..	4	1	4	5	0	200	Obese	200	Obese	Coma.	30 CH.	30 CH.	Faithful.	Died in coma, Sept., 1921.		
833	M Amer.	Druggist.	38	Sept., '21	Partial: downward progress	3	..	4	3	4	5	8	157	110	92	92	Drug addition.	25 protein for 2 weeks	10-5-700.	Faithful.	Died.	broncho-pneumonia, 1921.	
834	M Amer.	Child.	5	Sept., '21	None.	0	1	4	0	5	3	6	41	38	30	30	None.	30 protein for 7 weeks	30-20-940.	Faithful.	Good.	Normal blood sugar.	
835	M Heb.	Merchant...	50	Sept., '21	Partial.	4	..	4	4	4	5	3	142	190	176	161	None.	30 protein for 1 week	70-15-1600.	Faithful.	Good.	Normal blood sugar.	
837	M Amer.	Business...	41	Sept., '21	No glycosuria first 3 years. Intermittent since	5	..	5	5	5	5	11	175	226	155	147	None.	40 protein for 4 days	80-40-2000.	Faithful.	Good.		
839	F Amer.	Housewife...	43	Sept., '21	Partial.	3	..	5	3	5	5	5	143	148	97	82	None.	30 protein for 3 weeks	40-5-700.	Faithful.	Under treatment.	Severe case.	
840	M Heb.	Tailor.	63	Sept., '21	Glycosuria almost constantly	5	..	5	5	5	5	4	145	175	117	118	None.	30 protein for 1 month	170-20-1700.	Faithful.	Mistakes in diet recently.	Not heard from	
841	F Heb.	Housewife...	67	Sept., '21	Partial. Lax.	10	..	4	10	4	5	3	141	234	191	182	None.	40 protein, 10 CH for 1 week	10 CH-15.	Faithful.	Fair.	No glycosuria.	
843	M Heb.	School...	9	Sept., '21	None.	2	..	2	0	2	67	52	50	None.	30 protein for 1 week	135-5-600.	Unfaithful.	Broke diet constantly.	Lost from observation.	
844	M Amer.	Insurance...	64	Sept., '21	Restricted CH. Downward progress	6	..	4	6	4	190	115	108	Boils.	30 protein for 8 days	65-20-1700.	Faithful.	Gave up treatment.		

TABLE IV (Continued)

Case No.	Sex	Race	Occupation	Age at Admission	Date of Admission	Treatment Before Admission	Duration of Diabetes				Body Weight				Height	Complications	Initial Treatment	Final Diet, Protein, CH and Total Cal.	Degree of Fidelity	Result
							Before Admission		After Admission	Total	Pounds									
							Yr.	Mo.			Yr.	Mo.	Standard Normal	Before Admission						
							Yr.	Mo.	Yr.	Mo.	Yr.	Mo.	Yr.	Mo.						
845	F	Bel.	Housewife	35	Sept., '21	Partial	4	4	4	4	4	5	3	132	198	164	136	30 protein for 2 65-15-1200. weeks	Faithful	Good. Normal blood sugar.
846	M	Amer.	Hardware	29	Sept., '21	Restricted CH.	1	6	4	1	10	5	7	146	133	121	120	30 protein for 1 day.	Faithful	Good. Normal blood sugar.
847	M	Ger.	Fl.-list.	62	Sept., '21	Restricted CH.	8	4	4	8	4	6	0	184	225	108	155	Hypertension. Edema. Icterus.	Faithful	Good.
848	M	Bel.	Contractor	57	Sept., '21	Partial	5	3	5	3	5	7	157	184	161	154	Glaucome of toe	Faithful	Good. Normal blood sugar.	
849	M	Amer.	Print.	60	Sept., '21	Restricted CH.	12	4	4	12	4	6	0	184	218	156	143	Fibrous myocarditis. 2 weeks	Faithful	Follows diet partially.
852	M	Bel.	Merchant	54	Sept., '21	Discarded treatment	4	4	4	4	4	5	4	115	190	154	145	None	Faithful	Lost from observation.
856	M	Span.	Bank cashier	29	Sept., '21	Partial. Lax	4	4	3	4	5	4	134	116	90	88	None	Faithful	Good.	
857	M	Span.	Lawyer	77	July, '21	Partial	1	4	6	1	0	4	11	133	167	122	152	None	Partial.	Hypertension. No glycosuria.
863	F	Amer.	Nurse	24	Sept., '21	Lax. Lost weight	2	4	2	4	5	4	126	120	90	81	None	Faithful	Abandoned diet.	
867	F	Bel.	Cashier	25	Oct., '21	Intermittent glycosuria	1	3	1	3	5	5	132	131	110	101	None	Faithful	No glycosuria. Tendency to hyperglycemia.	
869	F	Bel.	Housewife	46	Sept., '21	Partial. Restricted CH	1	4	1	4	5	7	155	200	180	170	Hypertension.	Faithful	Good. Low blood sugar.	
873	F	Bel.	Housewife	54	Sept., '21	Restricted CH	6	4	6	4	5	1	135	250	134	110	Hypertension. Hyperthyroidism	Faithful	Faithful. Mistake. Low blood sugar.	
874	F	Bel.	Housewife	55	Sept., '21	Partial	7	4	7	4	5	2	138	200	134	110	Hypertension.	Faithful	Severe case. Under treatment in Institute.	
878	F	Amer.	Clerk	47	Oct., '21	None	2	3	2	3	5	7	155	126	93	74	Neuritis.	Faithful	Severe case. Under treatment in Institute.	
881	M	Bel.	School	9	Oct., '21	Partial	2	9	3	3	9	4	2	60	88	48	45	None	Partial.	Good.
883	F	Amer.	Housewife	30	Oct., '21	None	0	1	3	0	4	5	5	136	148	118	113	None	Faithful	Good. Normal blood sugar.

884	F	Feb..	Housewife...	61	Nov.	'21	Glycosuria most of time	9	2	..	9	2	..	9	2	5	4	144	200	135	178	Hypertension.	40 protein for 1 week	80-20-1500	Faithful...	Fair.
885	F	Amer..	Housewife...	50	Oct.	'21	Disregarded diet..	2	..	3	128	90	90	None	Transgressed.	30 protein for 1 week	65-10-1400.	Unfaithful.	Charged doctors.
886	F	Feb..	Housewife...	40	Oct.	'21	None.	2	..	3	145	119	115	None	30 protein for 1 week	65-10-1400.	Faithful.	Good.	
889	F	Feb..	Housewife...	40	Oct.	'21	None.	2	..	3	145	119	113	Drug addict.	65 protein, 15 CH for 3 days	Unweighed.	Faithful.	Good.	
892	M	Feb..	Physician...	34	Nov.	'21	None.	6	..	2	173	168	155	Hypertension.	Low unweighed diet for 1 day	Unweighed.	Faithful.	Good.	
893	F	Feb..	Housewife...	60	Nov.	'21	Partial.	12	..	3	142	108	108	None	40 protein, 5 CH for 1 day	90-40-1800.	Faithful.	Good. Mistakes but no glycosuria.	
894	M	Feb..	Tailor.	32	Oct.	'21	None.	..	6	3	135	132	136	Acidosis.	20 protein for 2 weeks	40-10-750.	Faithful.	Excellent. No hyperglycemia.	
900	M	Feb..	Child.	4	Oct.	'21	None.	..	1	3	29	25	28	Hypertension.	30 protein for 2 days	70-20-1650.	Faithful.	Good. Normal blood sugar.	
902	F	Feb..	Housewife...	44	Sept.	'21	Partial.	6	..	4	250	133	133	Gout.	30 protein for 7 weeks	30-01-1300.	Faithful.	Good.	
903	F	Feb..	Housewife...	34	Sept.	'21	Glycosuria prevented.	2	..	4	140	130	112	None.	1000 calories for 2 days	30-50-1600.	Faithful.	Good. Normal blood sugar.	
905	M	Amer.	Physician...	55	Sept.	'21	No glycosuria since onset	..	6	4	200	162	152	None.	15 protein for 5 wks.	30-5-500.	Faithful.	Good. Normal blood sugar.	
911	M	Amer.	School.	15	Sept.	'21	Glycosuria most of time	1	..	3	130	98	87	None.	35 protein, 5 CH for 2 weeks	50-10-1200.	Unfaithful.	Abandoned treatment. Abortion performed Dec. 1921. Glycosuria. Gradual downward progress.	
915	F	Amer..	Housewife...	30	Sept.	'21	Partial.	1	..	4	133	96	94	Pregnancy.	35 protein, 5 CH for 2 weeks	50-10-1200.	Unfaithful.	Abandoned treatment. Abortion performed Dec. 1921. Glycosuria. Gradual downward progress.	
917	M	Amer..	Business.	32	Sept.	'21	Partial.	1	..	4	178	123	117	None.	30 protein for 13 days	50-15-1400.	Faithful.	Good.	
926	M	Amer..	Mfgt.	50	Oct.	'21	No glycosuria.	5	..	3	170	131	121	Pleurisy.	40 protein for 3 wks.	75-20-1800.	Faithful.	Good. Mistakes, but no glycosuria.	
927	M	Amer..	Druggist.	64	Oct.	'21	Restricted CH.	4	..	3	170	131	127	Carbuncle.	30 protein for 2 days	50-15-1400.	Faithful.	Good.	
928	F	Amer..	Nun.	62	Oct.	'21	Partial. No starches.	8	..	3	162	131	119	None.	40 protein, 5 CH for 1 week.	Unweighed.	Faithful.	Moderate hyperglycemia.	
932	M	Amer..	Soldier.	40	Oct.	'21	High calory diet.	2	..	3	215	123	100	Abscesses of thighs. Pulmonary Tbc.	30 protein for 3 wks.	65-15-1700.	Faithful.	Normal blood sugar. Invalid.	
936	M	Amer..	Physician.	42	July.	'21	Fair.	4	..	6	None.	40 protein, 5 CH for 1 day	80-40-2100.	Partial.	Careless. Unweighed diet.	
939	M	Amer..	Merchant.	58	Oct.	'21	Glycosuria past 3 years	5	..	3	178	141	136	None.	Complete fast for 3 days	80-40-2000.	Faithful.	Good. Normal blood sugar.	
947	M	Feb..	Merchant.	47	Oct.	'21	Partial.	2	..	3	210	120	120	Pulmonary Tbc.	30 protein for 7 days	40-5-700.	Faithful.	Changed treatment.	
949	M	Amer..	Physician.	55	Oct.	'21	Partial. Internic.	5	..	3	167	155	127	Cerebro-spinal syphilis.	40 portein for 5 days	65-20-1700.	Faithful.	Good.	
950	F	Amer..	Child.	3	Oct.	'19	None.	30	30	30	None.	CH and fat restricted	Unweighed.	Faithful.	Good. Mild case.	
951	F	Feb..	Housewife...	50	Oct.	'21	Partial. Constant glycosuria.	2	..	3	141	133	127	None.	30 protein for 3 days	75-25-1900.	Faithful.	Good. Normal blood sugar.	
953	F	Feb..	Housewife...	55	Nov.	'21	None.	3	..	2	127	124	121	Cataracts. Myocardial insufficiency	40 protein, 10 CH for 6 days	75-25-1400.	Faithful.	Good.	
955	F	Feb..	Housewife...	60	Nov.	'21	Restricted sugar and starch.	7	..	2	120	122	120	None.	30 protein for 3 days	70-20-1400.	Faithful.	Estimated diet. Mistakes. Gangrene of thumb.	
959	F	Amer..	Housewife...	40	Nov.	'21	None.	5	..	2	174	136	131	None.	100, cal. for 3 days.	Unweighed.	Faithful.	Good. Normal blood sugar.	

TABLE IV (Continued)

Case No.	Sex	Race	Occupation	Age at Admission	Date of Admission	Treatment Before Admission	DURATION OF DIABETES				HEIGHT		BODY WEIGHT			Complications	Initial Treatment	Final Diet, Protein, CH and Total Cal.	Degree of Fidelity	Result	
							Before Admission		Total		Ft.	In.	Pounds								
							Yr.	Mo.	Yr.	Mo.			Standard Normal	Before Admission	at Admission						
992	M	Heb.	Physician	42	Nov., '21	Partial	1	2	1	2	5	6	150	192	180	151	40 protein, 5 CH for 3 days	Unweighed.	Faithful	Good. Normal blood sugar.	
993	F	Heb.	Housewife	40	Nov., '21	None	4	2	2	6	5	1	130	204	182	160	40 protein, 5 CH for 1 week	80-15	Faithful	Under treatment. No hyperglycemia.	
994	F	Heb.	Housewife	39	Nov., '21	Restricted CH	3	2	3	2	5	1	126	174	140	135	40 protein for 5 days	70-20-1400	Faithful	Good. Normal blood sugar.	
995	F	Heb.	Housewife	57	Nov., '21	Restricted CH	6	2	6	2	4	10	129	153	123	119	35 protein, 5 CH for 6 days	85-20-1100	Faithful	Good. Normal blood sugar.	
970	M	Heb.	Office work.	17	Dec., '21	None	3	1	4	5	5	128	125	110	104	Complete fast for 3 days	Unweighed.	Faithful	Good.		
973	M	Amer.	Child	14	Dec., '21	None	5	1	6	2	94	24	22	20	20	Acidosis	0 protein for 10 days, 15 protein, 10 CH for 1 wk.	30-5	Faithful	Under treatment. Normal blood sugar.	
975	F	Amer.	Housewife	32	Dec., '21	Hyperglycemia	2	1	2	1	5	7	144	188	155	145	30 protein for 1 week	40-5-500	Faithful	Under treatment. Severe case.	
980	F	Heb.	Housewife	58	Dec., '21	None	7	1	7	1	5	7	157	186	155	145	10 protein, 5 CH for 2 weeks	50-5-900	Faithful	Good. Under treatment.	
983	F	Heb.	Child	6	Dec., '21	None	1	1	2	1	5	35	32	32	37	None	1,000 cal. for 1 day	75-60-1900	Faithful	Good. Mild case.	
984	M	Heb.	Carpenter	53	Dec., '21	None	7	1	7	1	5	6	149	181	154	150	Cataracts, Retinitis, Bld.	Unweighed.	Faithful	Good. Low blood sugar.	
985	F	Amer.	Clark	29	Dec., '21	None	4	1	5	5	4	129	136	119	119	None	300 cal. for 1 week.	30 protein.	Unfaithful	Under treatment. Mild case.	
987	F	Heb.	Housewife	38	Dec., '21	Partial	6	1	5	1	5	3	132	165	150	147	None	Unweighed.	Unfaithful	Good. No hyperglycemia.	
989	F	Amer.	Child	8	Dec., '21	None	1	1	1	1	4	51	47	47	46	Acidosis	20 CH	20 CH	Faithful	Under treatment.	
1002	F	Amer.	Housewife	64	Oct., '21	None	4	3	4	3	4	11	131	150	145	132	None	35 protein, 5 CH for 5 days	85-25-1700	Faithful	Good. Normal blood sugar.
1003	M	Heb.	Merchant.	40	Oct., '21	Partial	5	3	5	3	5	5	146	168	120	120	Pancreatitis, Jaundice, Anemia.	30 protein for 16 days	Faithful	Severe case. Tendency to hyperglycemia.	
1008	F	Hungarian	Housewife	52	Oct., '21	None	7	3	7	3	4	11	131	157	135	124	None	15 protein for 11 days	80-15-1400	Faithful	Hyperglycemia. Mistakes.
1009	M	Amer.	School.	17	Oct., '21	None	3	3	6	5	74	125	115	106	102	None	30 protein for 7 days	90-15-1400	Faithful	Excellent. Normal blood sugar.	
1011	F	Heb.	Saleswoman.	32	Oct., '21	None	4	3	7	5	1	123	149	130	131	Pruritus vulvae	30 protein for 1 day	85-45-2200	Faithful	Excellent. Normal blood sugar.	
1012	F	Amer.	Housewife	55	Nov., '21	Partial	9	3	9	3	5	148	160	127	128	Acidosis, Broncho-pneumonia	40 protein, 10 CH for 2 weeks	90-15-1200	Faithful	Good. Normal blood sugar.	
1016	M	Heb.	School	19	Nov., '21	Partial. Sugar-free until 6 mos. ago	2	2	2	2	5	1	119	90	80	63	None	20 protein for 1 mo. Then 10 protein for 5 weeks	30-4-600	Faithful	Under treatment. Normal blood sugar.
1018	F	Irish	Housewife	37	Nov., '21	None	6	2	8	5	3	132	210	210	205	Pruritus vulvae	40 protein, 5 CH for 3 days	90-20	Faithful	Under treatment. Normal blood sugar.	
1020	F	Irish	School	10	Nov., '21	None	3	2	5	4	7	72	75	58	60	None	40 protein, 15 CH for 1 day	80-25-1400	Faithful	Excellent. Goes to school. No hyperglycemia.	
1021	F	Heb.	Child	5	Nov., '21	Partial	11	2	1	1	3	6	41	50	40	40	None	25 protein for 9 days	40-20-900	Faithful	Excellent. No hyperglycemia.
1029	F	Amer.	Housewife	41	Nov., '21	None	5	2	7	5	2	133	182	126	115	Hyperextension	30 protein for 3 wks.	65-15-1600	Faithful	Good. Normal blood sugar.	
1030	M	Amer.	Engineer	49	Nov., '21	None	6	2	8	5	7	150	233	160	158	Mental depression	50 protein, 10 CH for 1 day	90-45	Unfaithful	Abandoned treatment.	
1032	F	Amer.	Housewife	50	Nov., '21	None	6	2	6	2	6	0	133	170	120	104	None	20 protein for 6 wks.	40-0-600	Faithful	Hyperglycemia.
1033	M	Amer.	Lawyer	56	Nov., '21	None	2	2	4	5	6	133	155	120	108	None	20 protein for 5 wks.	40-5-900	Faithful	Under treatment.	
1034	M	Amer.	Child	8	Nov., '21	Sugar-free first year. Constant sugar past 8 mos.	2	2	2	2	4	0	53	50	43	38	Acidosis	Glycosuria did not cease on a 2 weeks fast	40-0-800	Faithful	Total diabetes.

1038	F	German	Housewife	46	Nov., '21	Restricted CH.	6	..	2	6	2	5	4	142	152	140	Hypertension	40 protein for 8 days.	65-20-1300	Faithful	Good. Normal blood sugar.
1039	M	Amer.	Clerk	30	Nov., '21	Partial	..	5	2	..	7	5	7	149	155	115	None	30 protein for 2 wks.	50-15-1300	Faithful	Under treatment. Normal blood sugar.
1040	M	Heb.	Dry Goods	57	Nov., '21	Restricted CH.	..	8	2	..	10	5	6	153	210	160	Arterio sclerosis	40 protein, 5 CH for 3 wks.	80-40-2000	Faithful	Under treatment. Normal blood sugar.
1043	M	Amer.	Baby	1	Nov., '21	Partial	1 wk.	1	1	..	1	..	21	25	20	18	Acidosis	5 protein, 5 CH for 1 week.	10 protein.	Faithful	Abandoned treatment. Diet Dec. 22, 1921.
1044	M	Amer.	Physician	47	Nov., '21	Sugar-free first 2 1/2 years	3	..	2	3	2	5	11	177	168	126	None	30 protein for 4 wks.	70 - 5 - 400	Faithful	Under treatment.
1046	M	Amer.	School	12	Nov., '21	Sugar-free first 1 1/2 years	2	..	2	2	2	4	11 1/2	84	115	82	None	15 protein for 4 wks.	40 - 5 - 800	Faithful	Under treatment. Normal blood sugar.
1047	F	Amer.	Housewife	48	Dec., '21	None	1	..	1	1	1	5	5	146	170	152	Attacks of acidosis with vomiting.	1,000 cal. for 3 days.	65-20	Partial	Careless. Return of symptoms.
1048	F	Amer.	Housewife	45	Dec., '21	Constant glycosuria recently	6	..	1	6	1	5	10	166	170	96	None	30 protein for 2 wks.	45 - 5 - 500	Faithful	Under treatment in Institute.
1049	M	Amer.	Editor	49	Dec., '21	Partial	10	..	1	10	1	5	9	166	178	115	None	35 protein, 5 CH for 2 weeks.	65-20-1500	Partial	Under treatment. Normal blood sugar.
1050	F	Heb.	Housewife	52	Dec., '21	Restricted CH. Occasional glycosuria.	6	..	1	6	1	4	11	131	160	126	Neuritis	70 protein, 40 CH for 1 day.	50-10-900	Faithful	Under treatment. Mild case.
1052	F	Amer.	School	14	Dec., '21	Partial	..	1	1	..	2	5	3 1/2	107	103	94	Acidosis	20 protein for 4 days.	50-15-1300	Faithful	Excellent. Normal blood sugar.
1055	M	Irish.	School	10	Dec., '21	None	..	2	1	..	3	4	6 1/2	68	65	55	None	30 protein for 2 days.	50-10-1100	Faithful	Normal blood sugar. Goes to school.
1058	F	Amer.	Housewife	37	Dec., '21	Restricted CH	1	6	1	1	7	5	2	129	115	98	None	1 60 0cc for 1 day.	Unweighed.	Faithful	Good. Normal blood sugar.
1060	F	Amer.	Housewife	60	Dec., '21	Restricted CH.	4	..	1	4	1	5	7	157	208	170	Neuritis	40 protein, 5 CH for 5 days.	80-20	Partial	Incurant. Careless. Poor result.
1062	M	Heb.	Physician	61	Dec., '21	None	18	1	1	18	1	5	1	137	190	156	Neuritis	40 protein, 5 CH for 2 days.	Unweighed.	Faithful	Mild case. Under treatment.
1063	M	Amer.	Retired	76	Dec., '21	Restricted CH	1	..	1	1	1	5	9	167	188	94	Carbuncles. Sciatica	30 protein for 3 wks.	30 protein.	Faithful	Died of infection. Dec. 31, 1921.
1069	F	Heb.	School	15	Dec., '21	None	1	6	1	..	7	4	10	108	72	62	None	25 protein for 2 wks.	25 protein.	Faithful	Severe case. Under treatment.
1070	M	Amer.	Child	8	Dec., '21	Glycosuria past 5 months	1	10	1	1	11	40	24	Acidosis. Otitis media.	5 protein, 15 CH for 2 weeks.	10 protein.	Faithful	Severe case. Under treatment.
1073	M	Amer.	Civil Eng.	26	Dec., '21	Glycosuria past 2 years	5	..	1	5	1	5	10	158	148	112	None	30 protein	30 protein.	Faithful	Under treatment.
1074	M	Amer.	Musician	43	Dec., '21	None	2	..	1	2	6	..	181	165	125	134	Gall stones	30 protein	30 protein.	Faithful	Under treatment.

NUTRITIONAL FACTORS IN THE GROWTH OF YEASTS AND BACTERIA †

I. VITAMINES.

BY LOUIS FREEDMAN* AND CASIMIR FUNK.

*Biochemical Laboratory of Columbia University at the
College of Physicians and Surgeons, New York City,
and the Research Laboratory of H. A. Metz, New York City.*

INTRODUCTION.

Since the discovery of Wildier's yeast stimulating "bios" in 1901, rapid progress has been made in determining the nutritional requirements of various yeasts and bacteria.

The early work of many investigators has shown that both yeasts and bacteria require for their growth certain unknown substances, the properties of which correspond closely to those of our present day water-soluble B vitamine. Of late, however, considerable discussion has arisen regarding the identity of the substance that promotes the growth of yeast cells with that of vitamine B, and also its relation to the substance that stimulates the growth of bacteria.

In the present work, the authors have made an attempt to remove some of the uncertainties regarding these factors, and to show that a close nutritive analogy exists between yeasts and bacteria.

EXPERIMENTAL PROCEDURE.

A strain of hemolytic streptococcus, which was kindly furnished by Dr. Mueller,** was used. The medium for the growth

† Read before the Society for Experimental Biology and Medicine, New York City, February 15, 1922.

* Submitted by Louis Freedman in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in the Faculty of Pure Science, Columbia University, 1922.

** The authors are indebted to Dr. J. Howard Mueller of the Department of Bacteriology, College of Physicians and Surgeons, for the use of a strain of streptococcus, and for a description of the preparation of his media, and of the technique of carrying out the bacteriological tests.

of this organism was prepared as follows: A fresh beef-heart, devoid of fat, and finely chopped, was boiled for five minutes with an equal weight of distilled water; the infusion was strained through cloth and filtered, clear, through filter paper. This beef-heart infusion was boiled for 15 minutes with two percent of its weight of norit charcoal; the decolorized liquid (to be referred to hereafter as D. I.) was filtered clear, and mixed with an equal volume of a glucose-salt solution† (to be termed G. S.). This mixture was boiled for several minutes, filtered, adjusted to a p_h of 7.4 and sterilized in lots of 250 cc. at ten pounds pressure for ten minutes. This medium (referred to hereafter as D.I.-G.S.), inoculated with streptococcus, failed to give growth when used alone, whereas the original undecolorized heart infusion was favorable for the growth of this organism.

EFFECTS OF VARIOUS MEDIA ON GROWTH OF STREPTOCOCCI.

The tests on streptococci were made as follows: Duplicate tubes were prepared containing nine cc. of the D.I.-G.S. solution plus one cc. of the solution to be tested, one tube being inoculated and the other acting as a sterile control. One set of duplicate tubes of D.I.-G.S. alone, and another set containing this solution plus one percent peptone, were used as additional sterile and inoculated controls. The inoculations were made from a 24-hour bouillon culture previously inoculated from a pure blood culture.

The original undecolorized heart infusion gave a profuse growth when inoculated with streptococci, while the decolorized medium, either alone or together with the glucose-salt solution, failed to give growth. The decolorized medium, however, gave growth when one percent peptone was added to it, while one percent peptone solution alone or together with glucose-salt solution, failed to give growth. This confirms some of the results obtained by Mueller.¹

Autolyzed brewers' yeast, diluted 20 times, when added to the D.I.-G.S. medium, supported the growth of streptococci; but in some cases the growth was retarded, due probably to the strong acid reaction of the autolyzed yeast. When the re-

† The glucose-salt (G.S.) solution consisted of an aqueous solution of: NaCl—1.0%; CaCl₂—0.02%; MgSO₄—0.04%; K₂HPO₄—0.20%; Glucose (Difco)—0.20%.

action was adjusted to an alkaline range, (p_h of 7.4-7.8) a more uniform growth of the microörganism was obtained. An added factor may be the possible presence in autolyzed yeast of substances which are toxic to the specific organism. The above results are given in detail in table I.

TABLE I.

Growth of streptococci on various media.

No.	MEDIA	Growth
1.	10 cc. Undecolorized beef-heart infusion.....	+++
2.	10 cc. Decolorized beef-heart infusion.....	—
3.	10 cc. Glucose-salt solution (G. S.)	—
4.	10 cc. D. I.-G. S. solution	—
5.	10 cc. D. I.-G. S. solution containing 1% peptone.....	++
6.	10 cc. G. S. solution containing 1% peptone.....	—
7.	10 cc. 1% peptone solution alone.....	—
8.	9 cc. D. I.-G. S. + 1 cc. 5% autolyzed yeast	+
9.	9 cc. D. I.-G. S. + 1 cc. 5% autolyzed yeast (p_h 7.4-7.8)...	++

+++ Denotes profuse growth.
 ++ " moderate "
 + " slight "
 — " no "

EFFECTS OF THE SAME MEDIA ON THE GROWTH OF YEAST CELLS.

For the test on the growth of yeast cells, we followed the Funk-Dubin² method, which is the most convenient and which, briefly, is carried out as follows: A yeast suspension is prepared by shaking a loopful of a 48-hour pure yeast culture in 100 cc. Nägeli solution on a shaking machine for three hours. Duplicate sets of tubes are prepared containing

- (1) 4 cc. yeast suspension + 5 cc. Nägeli solution + 1 cc. water
- (2) 4 cc. yeast suspension + 5 cc. Nägeli solution + 1 cc. of the solution to be tested.

The tubes are incubated for 20 hours at 30°C. The contents of the tubes are then transferred to special centrifuge tubes, the bottom part of which is a capillary 2.5 cm. long and is graduated in millimeters. These tubes are centrifuged for 15 minutes at about 2500 R.P.M., and the growth of the yeast cells is read directly on the tube. The reading of tube 1, which constitutes the blank, is subtracted from that of tube 2 to give the net growth of yeast cells in millimeters. In all tests, conditions were maintained which precluded the possibility of bacterial contamination.

Undecolorized beef-heart infusion gives a growth of yeast cells which compares favorably with that produced by a 5% solution of autolyzed yeast itself. The addition of glucose to autolyzed yeast has very little if any additional activating property, other than that of slightly enriching the medium. One cc. of decolorized heart infusion when added to the Nägeli solution with or without the glucose-salt solution, has little or no effect on yeast cells; while the D.I.-G.S. medium containing one percent of peptone, when added to the Nägeli solution, stimulates the growth of yeast cells just exactly as much as when one percent peptone solution alone is added.

TABLE II.

Effects of various media on the growth of yeast cells.

No.	Substance added to 9 cc. of standard Nägeli solution	Net yeast Growth in mm.
1.	1 cc. 5% autolyzed yeast (5 cc. in 95 cc. water)	10.0
2.	1 cc. 5% autolyzed yeast + 1 cc. 10% glucose solution (Difco)	11.0
3.	1 cc. D. I. solution alone	0.
4.	1 cc. D. I.-G. S. solution	1.5
5.	1 cc. 1% peptone solution (Difco)	2.5
6.	1 cc. D.I.-G. S. solution containing 1% peptone.	4.0
7.	7 cc. G. S. solution	0.
8.	1 cc. G. S. solution containing 1% peptone.	2.0
9.	1 cc. Undecolorized meat infusion	7.5
10.	1 cc. Undecolorized beef-heart infusion	12.0

It is apparent from the results shown in tables I and II, that there is present in beef and beef-heart infusions, and in peptone and autolyzed yeast, a substance that shows comparable growth-stimulation on hemolytic streptococci and yeast cells. The question now naturally arises as to the nature of the substance that shows such a marked similarity of effect on these two organisms. From the standpoint of the favorable action on yeast cells, we are probably dealing here with one or more substances of the class of B vitamine. As for the growth-influencing action on streptococci, this either is due to a substance of an identical or similar nature; or, as suggested in the work of Davis,³ Rivers and Poole,⁴ and others, we are dealing with two unknown substances, one or both of which may belong to the class of vitamines. These authors found that certain organisms, particularly those of the hemophilic type, require two substances for growth, both of these

SHAKING OF AUTOLYZED YEAST WITH FULLERS EARTH AND NORIT.

Funk and Dubin⁵ have shown that at least two different substances can be separated from autolyzed yeast by means of shaking with fullers earth. By this method it is now possible to separate the vitamine active for yeast growth, which has been provisionally called "vitamine D", from the anti-beriberi or B vitamine.

Several preparations of autolyzed yeast were subjected to shaking with various amounts of both fullers earth and norit, as follows: The clear filtrate of autolyzed yeast, after removal of the protein by heat coagulation, was first shaken for three hours with 50 grams of fullers earth per liter, and filtered. The filtrate showed very little loss of growth-stimulating effect on yeast cells as compared with the original material, while there was no observable loss of stimulation on bacterial growth. This filtrate was again subjected to shaking with fullers earth, this time with 100 grams per liter. The filtrate from this shaking gave a yeast growth-increase about one half as great as that given by the original 5% autolyzed yeast solution. This filtrate gave as a rule no growth of streptococci, although in one or two cases a slight growth was obtained. This second filtrate was again shaken for three hours with 100 grams of fullers earth per liter, the filtrate from this final shaking having almost no stimulating effect on yeast growth and none on bacterial growth.

We obtained practically similar results by subjecting autolyzed yeast solutions to shaking with norit. The first filtrate after shaking with 50 grams of norit per liter was still strongly active on both organisms, while the second filtrate, obtained after shaking the first with 100 grams per liter, showed a slight effect on yeast growth, but was entirely negative on the growth of streptococci, as was to be expected. The third filtrate, obtained after again shaking the previous filtrate with 100 grams of norit per liter, had lost all activity on the growth of both organisms.

A few experiments were also tried with Lloyd's reagent, the results comparing favorably with those obtained with the other two adsorbing reagents, although Lloyd's reagent is less energetic an adsorber than fullers earth or norit.

EXTRACTION OF THE ADSORBED MATERIAL FROM FULLERS EARTH AND NORIT BY MEANS OF BARYTA AND ACETIC ACID RESPECTIVELY.

Following the method of Seidell,⁶ the fullers earth containing the adsorbed vitamine-like material was shaken for two to three minutes with one and a half volumes of a 10% solution of baryta at 60°C. The solid was then filtered off, washed with water, and the combined filtrate and washings quickly neutralized with 20% sulphuric acid. The filtrate, after removal of the barium sulphate, was concentrated in vacuum and made up to a volume equal to the original volume of the medium before treatment with the adsorbing agent. The solution was then adjusted to a p_h of 7.4 and sterilized. Unless otherwise noted, one cc. of the solution was used in all tests.

The baryta extract of the fullers earth from the first shaking with autolyzed yeast (50 grams per liter) showed a comparatively strong growth stimulating action on the growth of both yeast cells and streptococci, as can be seen in table IV below. This extract contains nearly all of the vitamine B from autolyzed yeast and a small part of the newly isolated vitamine D. Its stimulating effect on yeast growth compares with that obtained by Funk and Dubin^{1,5} as shown in the second column of table IV. It also showed a comparatively strong stimulation of the growth of bacteria.

The baryta extract of the fullers earth from the second shaking with autolyzed yeast (100 grams per liter) had an effect on yeast growth almost equal to that of the first baryta extract; while the action on the growth of streptococci was only slightly diminished as shown by 2 (a) and 3 (a). This extract had no curative effect on polyneuritic pigeons, showing the apparent absence of vitamine B. The fullers earth, during the third shaking, failed to extract any more of the active substance, as its baryta extract showed no effect on yeast and bacterial growth.

Extraction of the norit with acetic acid: Following the method of Eddy, Stevenson, Johnson and Heft,⁷ the material adsorbed by the charcoal was extracted from it by heating the charcoal on a water bath for three hours with ten parts (by weight) of glacial acetic acid; the solution was filtered, and evaporated in vacuum to dryness; the residue was taken up in water, and the solution again evaporated. This procedure

was repeated several times to remove most of the acid. The last traces of acetic acid were neutralized by addition of normal sodium hydroxide solution. The neutralized solution was made up to a volume equal to the original volume of the autolyzed yeast, adjusted to the proper p_h (7.4) and sterilized. One c.c. of this extract was used in each test.

These acetic acid extracts from the charcoal gave very interesting results. As shown in table IV, Nos. 5 (a) and 6 (a), they are practically in accord with the results obtained from the baryta extracts from the fullers earth after adsorption of the vitamine-like substance. The first two extracts stimulate both yeast and bacterial growth, while the extract from the third shaking [7 (a)] shows a very slight stimulating effect on yeast growth and no effect on the growth of streptococci.

TABLE IV.

Effect of Shaking of Autolyzed Yeast with Fullers Earth and Norit.

No.	FULLERS EARTH	Net Yeast Growth* in mm. obtained by		Bac- terial growth
		Funk and Dubin	Ourselves	
1.	Autolyzed yeast (5% solution)...	14.5	12.5	++
2.	Autolyzed yeast shaken with 50 grams per liter.....	12.0	9.5	++
2 (a)	Baryta extract of fullers earth (from 2)	4.0	5.5	++
3.	Autolyzed yeast (filtrate from 2) shaken with 100 grams per liter	6.0	5.0	—
3 (a)	Baryta extract of fullers earth (from 3)	3.5	4.0	++
4.	Autolyzed yeast (filtrate from 3) shaken with 100 grams per liter	0.5	0.5	—
4 (a)	Baryta extract of fullers earth (from 4)	0.	0.	—
NORIT				
5.	Autolyzed yeast shaken with 50 grams per liter.....	13.5	10.5	+
5 (a)	Acetic acid extract of norit (from 5)	3.0	4.0	+
6.	Autolyzed yeast (filtrate from 5) shaken with 100 grams per liter	3.0	3.0	—
6 (a)	Acetic acid extract of norit (from 6)	3.0	3.0	+
7.	Autolyzed yeast (filtrate from 6) shaken with 100 grams per liter	0.5	0.	—
7 (a)	Acetic acid extract of norit (from 7)	0.	1.0	—

* Slight variations between the results obtained by Funk and Dubin and by ourselves are due to the use of different preparations of autolyzed yeast.

Our results as detailed in table IV, show that we can obtain from autolyzed yeast by fractional adsorption with fullers earth and norit, and subsequent extraction of the adsorbents, a concentrated solution of vitamine D, almost free from vitamine B. This vitamine D extract is active in stimulating the growth of both yeast cells and streptococci, but is not curative for beriberi. We were, however, unable to obtain vitamine B entirely free from D as this fraction which was found to be curative for beriberi was also active in stimulating the growth of yeast cells and bacteria. We have also shown that the extraction of these materials from the adsorbents with baryta and acetic acid is almost quantitative.

SHAKING OF BEEF-HEART INFUSIONS WITH FULLERS EARTH AND NORIT

A beef-heart infusion, prepared as described in the early part of this paper, when shaken for three hours with 50 grams of fullers earth per liter, lost most of its stimulating effect on yeast growth, while it still retained enough of the active substance to promote the growth of streptococci. The filtrate, after a second shaking with fullers earth, (100 grams per liter) showed no activity on the growth of either yeast or bacteria.

The baryta extract of the fullers earth from the first shaking, peculiarly showed only a very slight growth-stimulating activity on yeast; even the addition of 2 cc. of the extract to the medium increased the growth of yeast cells only slightly. The baryta extract of the fullers earth from the second shaking was correspondingly less active on yeast growth, showing a net growth of only 1 mm.; while it was only slightly active on bacterial growth. The effects on the two organisms, however, were comparable, as shown in table V.

Norit removed from beef-heart infusions practically all of the substance which stimulates the growth of yeast when the infusion was shaken with 2% of its weight (approximately 20 grams per liter) for three hours. The infusion was, however, still effective for the growth of streptococci. A second shaking, this time with 50 grams per liter, removed all activity on yeast and bacterial growth.

The acetic acid extract of the norit from the first shaking showed great growth stimulation on both organisms, this extract giving almost as much stimulation as the original medium. The net growth stimulating activity of the extract on

yeast varied from 5.5 to 9 mm. with an average of about 7.5 mm. This activity compared favorably with that of 1% peptone solutions. Extraction of the norit from the second shaking failed to give any action on yeast or bacteria. Table V gives in detail the results of these extraction experiments with beef-heart infusions.

An interpretation of these results shows that the growth-stimulating substances are present in smaller amounts in beef-heart infusions than in autolyzed yeast; and that they are more easily adsorbed from the former than from the latter. This adsorption is more complete, at least from beef-heart infusions, with norit than with fullers earth. Baryta fails to extract any active substance from the norit after adsorption, while glacial acetic acid is ineffective on fullers earth.

TABLE V.

Effect of Shaking of Beef-Heart Infusions with Fullers Earth and Norit.

No.	FULLERS EARTH	Net Yeast growth in mm.	Bacterial growth
1.	Beef-heart infusion — 1 cc. (equiv. to 2/5 gm. beef-heart)	12.0	++
2.	Beef-heart infusion shaken with 50 gms. per liter 1 cc.	3.0*	++
2 (a)	Beef-heart infusion shaken with 50 gms. per liter 2 cc.	3.5*	
2 (b)	Baryta extract of fullers earth (from 2) 1 cc.	1.0	+
2 (c)	Baryta extract of fullers earth (from 2) 2 cc.	1.0	+
3.	Beef-heart infusion (filtrate from 2) shaken with 100 grams per liter, 1 cc. ...	0.	—
3 (a)	Beef-heart infusion (filtrate from 2) shaken with 100 grams per liter, 2 cc. ...	0.	—
3 (b)	Baryta extract of fullers earth (from 3) 1 cc.	1.0	+
3 (c)	Baryta extract of fullers earth (from 3) 2 cc.	1.0	+
NORIT			
4.	Beef-heart infusion shaken with 20 grams (2%) per liter, 1 cc.	0.	+
4 (a)	Acetic acid extract from norit (from 4) 1 cc.	7.5*	++
5.	Beef-heart infusion (filtrate from 4) shaken with 50 grams per liter, 1 cc.	0.	—
5 (a)	Acetic acid extract of norit (from 5) 1 cc.	0.	—

* Average result of several extractions.

It is quite possible that the nature and reaction of the media play an important rôle in these adsorption experiments. Inhibiting substances may also be present, so that a solution may be active after adsorption, although inactive before that procedure. How important this hypothesis is, we cannot at present state, as we did not fully investigate these solutions before extraction with the adsorbents.

A summary of the results obtained shows that the substances which promote the growth of bacteria and yeast (as extracted from beef-heart, peptone, autolyzed yeast, etc) belong to the class of vitamins of the water soluble B type, but are not identical with B vitamin; that they are comparable in activity and show similar properties in that they are easily extracted from their natural sources by the same adsorbents, and are again readily recovered from these adsorbents without appreciable loss in activity. These results point strongly to the conclusion that they are either identical with vitamin D, or so similar to it in their physiological behavior, that only by actual isolation, purification, and complete chemical analysis will it be possible to differentiate them.

The separation of these vitamin-like substances from the bulk of impurities with which they are associated in nature, by adsorbing them in fuller's earth and norit and their subsequent extraction by chemical treatment of the adsorbents, gives us these unknown substances in a highly concentrated and comparatively pure form. This procedure is a distinct advantage over working with these substances in their natural media.

SUMMARY OF CONCLUSIONS

1. There are present in beef and beef-heart infusions, peptone and autolyzed brewer's yeast, certain substances which show a strong growth-stimulating activity on both hemolytic streptococci and yeast cells.
2. These active substances can be extracted from their natural sources by shaking with certain adsorbents, such as fuller's earth and norit charcoal, and can be recovered by extracting the adsorbents with baryta and acetic acid respectively.
3. The properties of these substances show them to be of a vitamin-like nature; and they are either identical with the

vitamine D described by Funk and Dubin⁵ or of a similar nature.

4. There is also present in beef and beef-heart infusions another substance which is necessary for the growth of hemolytic bacteria, and this substance is thought to be associated with hemoglobin.

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NUTRITIONAL FACTORS IN THE GROWTH OF YEASTS AND BACTERIA *¹

II. PROTEIN HYDROLYSATES.

By LOUIS FREEDMAN AND CASIMIR FUNK.

*Biochemical Laboratory of Columbia University at the College of Physicians and Surgeons, New York City
and the Research Laboratory of H. A. Metz, New York City.*

INTRODUCTION.

The use of proteins and protein hydrolysates for enriching culture media for the growing of bacteria is well known; and we find proteins to be a definite constituent of many culture media. Bainbridge¹ showed that certain bacteria required proteins for growth, while Robinson and Rettger² used a casein hydrolysate to enrich bacterial media. However, the cases in which it has been definitely shown that the growth of the bacterial organisms was due to the presence of the protein alone or to any of its hydrolytic cleavage products, are extremely rare. In most cases it has been shown that vitamins were present as an added constituent or as an adhering impurity.

The possible presence in proteins of a hitherto unknown substance which is now thought to be of biological importance in nutrition, has of late been suggested by several investigators. In this connection, Mueller³ thought that the growth-stimulating substances for hemolytic streptococci, which he obtained from certain proteins, were definite constituents of the protein molecule, and he described the isolation of two such substances from a preparation of enzyme-digested milk proteins called "aminoids". After his final precipitation of these substances, however, he found them to be inactive. Goy⁴

* Submitted by Louis Freedman in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in the Faculty of Pure Science, Columbia University, 1922.

¹ Read before the Society for Experimental Biology and Medicine, New York City, February 16, 1922.

also described the isolation, from certain fungi, of a nitrogen-free acid which he claimed stimulated the growth of bacteria and yeast, but he also found the finally purified substance to be inactive.

In a previous communication⁵ we have shown that we can obtain from beef and beef-heart infusions, peptone and autolyzed brewer's yeast, by adsorption with fullers earth and norit charcoal, certain substances which show a strong growth-stimulating activity on yeast cells and hemolytic streptococci. We have also shown that these substances can be extracted from their combination with fullers earth and charcoal by treating these adsorbents with baryta and glacial acetic acid respectively. The properties of these substances were found to be similar to those of the vitamine D described by Funk and Dubin⁶.

In the following work, the authors have tried to show the relationship between the substances found in proteins, and vitamine D; and that these substances are not present in purified proteins in general but are found associated only with certain proteins.

EXPERIMENTAL PROCEDURE.

For this work we have prepared a series of well known proteins, consisting of twelve animal and ten vegetable proteins. The proteins of animal origin varied to a great extent, and included the milk proteins, casein and lactalbumin, three ox-blood proteins, three egg proteins, muscle protein, liver albumin and globulin, and gelatin.

For the proteins of vegetable origin, we have prepared edestin (from hemp seed), the wheat and corn proteins, the three proteins from the pea, oryzenin (from rice), hordein (from barley), and yeast protein. These proteins were prepared according to the standard published methods, particular care being taken to have the proteins, in so far as it was possible, free from vitamins.

HYDROLYSIS OF THE PROTEINS.

All of the above proteins were hydrolysed by boiling them with seven parts of concentrated hydrochloric acid (specific

gravity 1.19) for eight to ten hours. After cooling, the humin substance was filtered off and the filtrate evaporated to dryness in vacuum. The residue was taken up in water and the solution again evaporated to dryness. This operation was repeated twice, making four evaporations, to remove the bulk of hydrochloric acid. The remaining acid was then neutralized by addition of normal sodium hydroxide; the solution was made up to a volume corresponding to a 10% solution of the protein, adjusted to a p_h of about 7.3 and sterilized at ten pounds pressure for ten minutes.

EFFECT OF THE PROTEIN HYDROLYSATES ON THE GROWTH OF STREPTOCOCCI.

The procedure for testing the effect of the hydrolysates on bacterial growth was the same as described in our previous paper⁵. One c.c. of the hydrolysate was added to the sterile D.I.-G.S. medium and the whole, after suitable inoculation, incubated at 37°C. for 24 hours. Of the animal proteins tested, only two, casein and commercial gelatin, gave a definite positive stimulation to the growth of streptococci, while fibrin and lactalbumin gave only a slight activity. Sulphuric acid hydrolysates of casein were also strongly active. Of the hydrolysates of the proteins of vegetable origin, we found only two to support the growth of streptococci, — namely, edestin and yeast protein.

TABLE I.

Effect of Protein Hydrolysates on Growth of Streptococci and Yeast.

No.	Hydrolysates of Animal Proteins. 1 cc. used.	Net yeast growth in mm.	Bacterial growth
1.	Casein (Purified) HCl hydrolysate.....	1.0	+
2.	“ “ H ₂ SO ₄ “	0	+
3.	“ (Technical) HCl “	1.0	+
4.	Lactalbumin	0.5	+
5.	Fibrin	—	—
6.	Serum globulin.....	—	—
7.	Serum albumin.....	—	—
8.	Beef-heart (muscle) protein.....	—	—
9.	Egg globulin.....	0	—
10.	Egg albumin.....	—	—

TABLE I. (*Continued*)

11. Vitellin (Egg yolk).....	0	+
12. Liver globulin (Beef).....	—	—
13. Liver albumin “.....	—	—
14. Gelatin (Commercial — Silver Label Brand) ..	—	+
15. Gelatin (Prepared from bones and marrow) ..	—	—
16. Gelatin (Prepared from bones without marrow)	—	—

Hydrolysates of Vegetable Proteins. 1 cc. used.

17. Edestin (Hemp seed).....	—	+
18. Gliadin (wheat)	—	—
19. Zein (corn)	—	—
20. Glutelin (corn).....	0	—
21. Legumin (Peas).....	0	—
22. Vicilin (Peas).....	0	—
23. Legumelin (Peas).....	0	—
24. Oryzenin (Rice).....	0	—
25. Hordein (Barley).....	0	—
26. Yeast protein	1.0	+

+ denotes growth.

± denotes slight growth.

— (under Bacterial column) denotes no growth.

0 (under Yeast column) denotes that growth was same as control.

— (“ “ “) “ inhibition.

Quantitative Results: We attempted to devise a method for the determination of the amount of stimulation of the growth of streptococci by centrifuging the bacteria, as is done in the method for yeast described by Funk and Dubin.⁷ This procedure, however, was found to be impractical, due to the difficulty of stopping the growth of bacteria, and also because of the occasional precipitation of substances which were not due to bacterial formation.

A better method for comparative results was devised, based on the change in hydrogen ion concentration due to the fermentation of the glucose in the D.I.-G.S. medium by the streptococci. This change in hydrogen ion concentration was determined by means of the Sörensen⁸ indicator method, using the Clark and Lubs⁹ indicator set. Cole and Jordan¹⁰ used a similar method for diagnosis, by fermentation tests, of the gonococcus, meningococcus and other pathogenic organisms.

The variation in hydrogen ion concentration, in all of our tests, covered a range from a p_h of 7.4 to a p_h of 4.0. For this test, we prepared standard solutions consisting of mixtures of Na_2HPO_4 and NaH_2PO_4 for the alkaline range, and solutions

consisting of mixtures of acetic acid and sodium acetate, according to Walpole¹¹, for the acid range. With these standard solutions, we used the following indicators:

Phenol red, for p_h 8.0 — 6.8
 Brom thymol blue, for p_h 7.6 — 6.0
 Brom cresol purple, for p_h 6.9 — 5.2
 Methyl red, for p_h 6.0 — 4.4

Three-tenths cc. of the required indicator solution was added to 10 cc. of the standard solution. The colored solutions were then put into uniform test tubes and the tubes sealed. The tests were made as follows: Duplicate tubes were prepared, each containing 9 cc. of the D.I.-G.S. medium and 1 cc. of the protein hydrolysate. One tube was inoculated with the streptococci and the other kept sterile. Both tubes were incubated together. After twenty-four hours, 0.3 cc. of the indicator necessary, which was determined roughly by the amount of bacterial growth formed, was added to each tube and the resulting color compared with the standard tubes.

As we used a control check for each test, we found this method to be very convenient and fairly accurate for comparative results. We have for convenience tabulated the results obtained with our protein hydrolysates in their stimulating action on the growth of streptococci, in tables IIa and b.

TABLE II (a)

Quantitative Effect of Protein Hydrolysates on the Growth of Streptococci.

p_h of standard D.I.-G.S. solution = 7.3

No.	Hydrolysates of Animal Proteins. (1 cc. used in each test)	Growth	pH after incubation
1.	Casein (purified) HCl hydrolysate.....	+	5.8
1(a).	“(sterile control)...	—	7.3
2.	Casein (purified) H ₂ SO ₄ hydrolysate.....	+	5.3
2(a).	“(sterile control)...	—	7.0
3.	Casein (technical) HCl hydrolysate.....	+	5.8
3(a).	“(sterile control)...	—	7.3
4.	Lactalbumin	±	7.0
4(a).	“(sterile control).....	—	7.3
5.	Fibrin	—	7.3
5(a).	“(sterile control).....	—	7.3

TABLE II. (a) (*Continued*)

6.	Serum globulin.....	—	7.3
6(a).	“ (sterile control).....	—	7.3
7.	Serum albumin.....	—	7.3
7(a).	“ (sterile control).....	—	7.3
8.	Beef-heart (muscle) protein.....	—	7.2
8(a).	“ (sterile control).....	—	7.3
9.	Egg globulin.....	±	7.0
9(a).	“ (sterile control).....	—	7.3
10.	Egg albumin.....	—	7.3
10(a).	“ (sterile control).....	—	7.3
11.	Vitellin (Egg yolk).....	—	7.3
11(a).	“ (sterile control).....	—	7.3
12.	Liver globulin.....	—	7.2
12(a).	“ (sterile control).....	—	7.3
13.	Liver albumin.....	—	7.3
13(a).	“ (sterile control).....	—	7.3
14.	Gelatin (commercial).....	+	6.0
14(a).	“ (sterile control)....	—	7.2
15.	Gelatin (Prepared from bone and marrow).....	—	7.2
15(a).	Gelatin (Prepared from bone and marrow) (sterile control).....	—	7.3
16.	Gelatin (Prepared from bone without marrow).....	—	7.2
16(a).	Gelatin (Prepared from bone without marrow (sterile control).....	—	7.3

TABLE II (b)

No.	Hydrolysates of Vegetable Proteins.	Growth	pH after incubation
17.	Edestin	+	6.5
17(a).	“ (sterile control).....	—	7.3
18.	Gliadin	—	7.0
18(a).	“ (sterile control).....	—	7.1
19.	Zein	—	7.3
19(a).	“ (sterile control).....	—	7.3
20.	Glutelin (corn).....	—	7.0
20(a).	“ (sterile control).....	—	7.2
21.	Legumin	—	7.0
21(a).	“ (sterile control).....	—	7.2
22.	Vicilin	—	7.0
22(a).	“ (sterile control).....	—	7.2

TABLE II. (b) (*Continued*)

23.	Legumelin	—	7.3
23(a).	“ (sterile control)	—	7.3
24.	Oryzenin	—	7.0
24(a).	“ (sterile control)	—	7.2
25.	Hordein	±	7.0
25(a).	“ (sterile control)	—	7.3
26.	Yeast protein	+	4.9
26(a).	“ “ (sterile control)	—	7.3

These quantitative results confirm our first results, namely, that only two of our animal and two of our vegetable proteins contain the growth stimulating vitamine for streptococci in appreciable amounts. Of the proteins whose hydrolysates contain the active substances, yeast protein is by far the richest, with casein second, commercial gelatin closely following, and edestin containing the smallest amount of the active substance.

EFFECT OF PROTEIN HYDROLYSATES ON GROWTH OF YEAST.

The protein hydrolysates as described above were tested on yeast; and, with the exception of casein and yeast protein, all the hydrolysates either failed to stimulate, or actually inhibited, the growth of yeast cells. Even the action of casein and yeast protein hydrolysates were, however, practically negative, the net increase in growth of yeast cells due to the vitamine activity of the hydrolysates amounting to one mm. for each of these proteins.

These results are not at all surprising, as Vansteenberge (12) found that leucine, tyrosine and asparagine inhibited the growth of yeast cells but not of the lactic acid bacteria. All of our hydrolysed proteins contain large amounts of leucine, while most of them contain varying amounts of tyrosine and aspartic acid.

A close analysis of the results obtained with these proteins together with their method of purification and their physical structure will, if anything, tend to confirm our view that the growth-stimulating action is due, not to any constituent part of the protein molecule, but to the tendency of the protein to adsorb vitamine and hold on to it in spite of all attempts at purification. Thus, yeast protein, the hydrolysate of which gave considerable stimulation to the growth of

streptococci, was obtained from a medium which we know to be very rich in vitamine, particularly the newly isolated vitamine D. This protein was prepared by heating the filtered autolyzed yeast until the protein had coagulated. As this protein separates in a form similar to milk curd, we see the possibility of great adsorption of vitamins. Although this protein underwent considerable washing, and was suspended in a dialyzing bag for several days, it still retained most of the vitamine which it had originally adsorbed.

The same is true of casein. This protein, which is precipitated by means of dilute acid and is purified by repeatedly redissolving and reprecipitating, separates at the start in the form of a coagulum, and, as other investigators have shown, has great adsorbing powers.* Consequently, no amount of redissolving and reprecipitating will entirely free it from vitamins, as its physical structure and adsorbing properties remain the same.

With gelatin, we have a somewhat analogous situation. Gelatin, which we prepared in the laboratory, from bones with and without the marrow, was entirely freed from vitamins by the process of purification described by Van Name.¹⁴ This consists, essentially, in precipitating the gelatin in absolute alcohol, extracting with ether, redissolving the protein in water, concentrating the solution to a jelly, reprecipitating in absolute alcohol and again extracting with ether. Commercial gelatin, (Silver Label Brand) however, contains enough of the active substance to stimulate the growth of streptococci, as we have shown in tables I and II. It seems apparent therefore that the present commercial process for purifying gelatin is not adequate for freeing this protein entirely from the vitamins contained in the bones and parts of the hide that are used. In this connection it might be mentioned that Boyer¹⁵ used an hydrochloric acid extract of finely divided bones for the cultivation of streptococci.

With edestin, we have a protein which was prepared in a somewhat different manner. We prepared this protein by extracting the ground hempseed with five percent sodium

* The following far-reaching statement was made by Prof. F. G. Hopkins¹³ in his Chandler Lecture given at Columbia University, 1921. "It is remarkable what a considerable portion of the vitamins present in milk is adsorbed by precipitated casein. A failure to recognize this has often obscured the results of feeding trials."

chloride solution at 60°C. The solution was allowed to cool gradually when the edestin separated as a crystalline precipitate. It was purified by redissolving in warm saline solution and again cooling the solution. Apparently, edestin also has great adsorbing properties. Osborne, Wakeman and Ferry¹⁶ were unable to free edestin entirely from vitamine.

Regarding the proteins, the hydrolysates of which showed no growth stimulating activity, a review of their methods of preparation and purification may throw some light on this point. Thus the prolamines, e.g., wheat gliadin, zein and hordein from cereals, were all extracted by means of hot alcohol, the alcoholic solutions evaporated to small volumes and the protein precipitated either in water or very dilute salt solutions. As the water soluble vitamins are also soluble in alcohol, we can readily see how all or nearly all of the vitamins would remain in solution. Those proteins, such as the albumins and globulins, which were salted out either by half saturation or complete saturation with ammonium sulphate were all purified by dialysis, and we know that vitamins are dialysable. Thus it is possible that these albumins and globulins have very little adsorbing properties, and therefore can be freed from vitamins by thorough purification. The same apparently holds true for the vegetable globulins with the exception of edestin.

The glutelins probably were free from vitamins even before extraction with dilute alkali, as they were obtained from the cereal residues after the extraction of the gliadins by means of alcohol. At any rate, the vitamins, if present would probably be destroyed by the continued action of the alkali.

The active proteins, from published analyses, show nothing in common that cannot be shown to apply to the other, inactive, proteins, so that we can safely rule out the question of amino acids or nitrogen content.*

* McLeod and Wyon¹⁷, in a recently published report on the "Supposed importance of vitamins in promoting bacterial growth," used among other extracts, alcoholic extracts of the kidneys of the guinea pig, and they believed that the growth was due to vitamin B, although they stated that the amino acid content of the extracts was also a factor. They also obtained better results with hydrolysed casein than with casein. They also found that "marmite", which is supposedly rich in vitamins, was inactive for the pneumococcus and meningococcus, and that charcoal, devoid of vitamins, when suspended in their bouillon cultures, stimulated the growth of these two organisms. The part of the work of these authors dealing with charcoal and "marmite" will no doubt need confirmation.

In summarizing the above results, three points stand out in explanation of the growth stimulating power of the hydrolysates of proteins.

- 1) The source of the protein; whether it is obtained from a medium rich in water-soluble vitamins of the B type such as Vitamin D.
- 2) The physical structure of the protein and its ability to adsorb vitamins.
- 3) The method of purification.

EXPERIMENTS WITH NEUTRAL SODIUM CASEINATE.

If these active substances present in casein and three of the other proteins, as described, are nothing more than adsorbed vitamins, and if the protein could be brought into solution without subjecting it to hydrolysis, then the vitamins would also go into solution and could be removed by adsorbing it with fuller's earth or some other adsorbing agent.

To test this theory, we prepared a solution of neutral sodium caseinate by suspending our purified casein in water, and adding five percent sodium hydroxide solution until the casein had practically all dissolved. A small amount of insoluble denatured casein, formed by the action of the alkali, was filtered off, and the solution was then made neutral to litmus. This neutral sodium caseinate solution (containing about 5% casein) was shaken for three hours with ten grams (50 grams per liter) of fuller's earth.

After shaking, the fuller's earth was separated from the solution by centrifugation, as filtration was very slow due to the formation of an emulsion, and the supernatant liquid was then filtered. The fuller's earth was repeatedly washed with water and centrifuged to remove small amounts of sodium caseinate adhering to it, pressed out on a suction filter, washed with alcohol and dried. This fuller's earth was then extracted with baryta and worked up as described in paper I.⁵ The resulting solution was made up to a volume corresponding to a ten percent solution of the original casein, adjusted to a p_h of 7.4 and sterilized. This solution, when tested, was found to have a strong stimulating effect on the growth of streptococci, but had no action on the growth of yeast cells.

The neutral sodium caseinate solution, after shaking with

fullers earth, was subjected to hydrolysis by adding concentrated sulphuric acid until a 30% solution was obtained and boiling for 36 hours. This hydrolysate failed to give any growth stimulating activity on either streptococci or yeast.

It is therefore apparent that most or all of the vitamine was removed from the casein as described. This shows that the active substance in the protein is not necessarily a constituent part of the protein molecule, and does not have to be isolated by breaking up the protein.*

SUMMARY OF CONCLUSIONS.

1. We can obtain from purified casein, commercial gelatin, yeast protein and edestin, by hydrolysis of these proteins, certain substances which show marked growth stimulating activity on hemolytic streptococci. Hydrolysates of purified egg globulin, lactalbumin and hordein, show traces, whereas hydrolysates of the other proteins examined are devoid of these activating substances.

2. We have found that these active substances are not a constituent part of the protein molecule, and that the amount of the substances present in the protein depends on the physical and adsorptive properties of the protein and the method and degree of purification.

3. The properties of these active substances, as obtained from the proteins described above, show that they are probably related to if not identical with the water-soluble vitamins obtained from brewers' yeast, particularly vitamine D.

4. We have described a method for determining the amount of these active substances by the use of Sørensen's indicator method, which is based on the change in hydrogen ion concentration due to the fermentative action of the bacteria. This method is advocated for comparative results only, and not as a direct quantitative method.

* The experiments with neutral sodium caseinate, just described, may be of practical importance in that they may lead to a method of preparing a vitamine-free casein. The casein thus obtained gives positive tests for all the color reactions known for the various amino acids, while its nitrogen content is the same as that of the original casein from which it was prepared. Further work is now in progress on this problem.

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A COMPARISON OF THE NITROGENOUS METABOLISM DURING SINGLE AND FRACTIONAL FEEDINGS.*

BY ALFRED CHANUTIN AND LAFAYETTE B. MENDEL

[*From the Sheffield Laboratory of Physiological Chemistry in Yale University, New Haven, Conn.*]

Whether there is a difference in the utilization of a definite amount of food depending on the rate at which it is furnished to the organism is obviously a matter of importance. The problem may be stated specifically by asking what difference, if any, the administration of the day's ration in a single or several divided portions may bring about in the metabolism. It is conceivable, for example, that the smaller portions would be more readily digested by the available alimentary secretions and thus promote better absorption. Again, the distribution of products of digestion to the organism over a relatively long period, instead of a single contribution of concentrated food derivatives, might render them more easily retained and might avert a loss of desirable nutrients through the increased katabolism brought about by a relatively sudden plethora of absorbed products.

A review of the literature (1) discloses conflicting claims of both decreased and increased utilization of protein after the partition of the day's food. The reported results of the investigations of the protein metabolism indicate inconsistencies which may be ascribed to several factors, the most important being the widely varying quantities of food given by the different observers, coupled with the fact that the diet, usually meat, was poorly balanced. The unjustifiable significance attached to small variations in the experimental data, together with the inadequacy of the control periods, has led to erroneous conclusions. An investigation was accordingly undertaken to study the effect of the partition of diets rich and poor respectively, in protein, on the nitrogenous metabolism.

Three bitches were kept in metabolism cages on a constant

* Part of the expenses of this study was defrayed by a grant from the Russell H. Chittenden Research Fund for Physiological Chemistry.

diet of commercial casein, lard, butter fat, dried yeast, sugar, bone ash, and salt mixture.*

This ration, containing a suitable protein, and vitamins A and B, is an excellent one for metabolism work. The vitamin B in the dried yeast maintained the appetite so that no difficulty was encountered in refusal to eat the food. (2, 3) Water was given *ad libitum*. The dogs were catheterized once daily; and the feces were marked off by carmine. The total nitrogen content of the urine and feces was determined by the Kjeldahl-Gunning method.

In each series the total daily diet was unvaried with respect to its composition, i.e., calorific value and content of nitrogen, salts, vitamins, etc. As soon as the daily nitrogen output became constant, the special experimental periods were begun. During the first and third periods the food was offered and always promptly consumed in a single meal. In the second period the food was divided into equal small portions, each of which was fed at intervals of one-and-one-half hours over a period of twelve hours.

The detailed results of our study are summarized in the appended tables.

It might be expected that if the frequent administration of food in smaller quantities promotes a continuous flow of digestive juices, the utilization of nitrogen would be promoted and the nitrogen balance become more favorable. This might be particularly emphasized under the conditions of unfavorable nitrogen balance due to inadequate protein intake.

The results obtained in three experiments (Tables I, II, III), in which the dogs were in negative nitrogen balance, failed to demonstrate any significant variations as a result of fractional feeding. In tables IV and V, which present observations on the effects of partition of high-nitrogen diets, there are likewise no noteworthy differences in the comparable experimental periods.

Table VI summarizes the daily averages of the different experiments.

* The salt mixture was prepared according to the suggestion of Karr: (2)

Sodium chloride.....	10 grams
Calcium lactate.....	4 "
Magnesium citrate.....	4 "
Ferrie citrate.....	1 "
I-KI solution.....	a few drops

A comparison of the nitrogen outputs and nitrogen balances in dogs on the same food intakes during periods in which the ration was fed in single or divided portions, respectively, fails to reveal any significant variations attributable to the mode of feeding, although the protein intakes were selected to represent a wide range of nitrogen intake (0.25 to 1.1 gm. per kilogram of body weight).

TABLE I

*Dog I.**Diet Low in Nitrogen*

	gm.
Casein (11.8%N.)	11.5
Sugar	45.0
Lard	22.5
Butter Fat	2.5
Bone Ash	3.0
Salt Mixture	2.0
Dried Yeast (8.0%N.)	3.0

1.6 gm. N.

450 Calories (estimated)

Period I

Day	Body weight kgm.	Nitrogen intake gm.	URINE vol. c.c.	Nitrogen gm.	Feces Nitrogen gm.	Total N. output gm.	Nitrogen Balance gm.
1	7.0	1.62	390	1.58	.52	7.00	—.58
2	6.9	1.60	350	1.60			
3	6.9	1.60	370	1.63			
4	6.8	1.60	370	1.67			
Average per day		1.60	370	1.62	.13	1.75	—.15

Period II

5	6.7	1.62	160	1.86	3.40	19.90	—3.88
6	6.7	1.60	140	1.78			
7	6.7	1.60	200	1.68			
8	6.7	1.60	180	1.65			
9	6.7	1.60	160	1.59			
10	6.7	1.60	160	1.47			
11	6.7	1.60	200	1.58			
12	6.6	1.60	160	1.63			
13	6.6	1.60	140	1.52			
14	6.6	1.60	270	1.74	.34	1.99	—.39
Average per day		1.60	177	1.65			

Period III

15	6.5	1.62	305	1.91	1.65	10.13	—2.11
16	6.5	1.60	245	1.54			
17	6.5	1.60	420	1.50			
18	6.5	1.60	260	1.62			
19	6.5	1.60	350	1.91			
Average per day		1.60	316	1.70	.33	2.03	—.42

TABLE II

*Dog II.**Diet Low in Nitrogen*

	gm.	
Casein (11.8%N.).....	13.5	1.83 gm. N. 540 Calories (estimated)
Sugar	45.0	
Lard	31.5	
Butter Fat	3.5	
Bone Ash	3.0	
Salt Mixture	2.0	
Dried Yeast (8.0%N.)....	3.0	

Period I

Day	Body weight kgm.	Nitrogen intake gm.	URINE		Feces Nitrogen gm.	Total N. output gm.	Nitrogen Balance gm.
			vol. c.c.	Nitrogen gm.			
1	7.9	1.85	130	2.31	3.33	23.41	—6.92
2	7.8	1.83	110	2.25			
3	7.8	1.83	95	2.25			
4	7.8	1.83	130	2.25			
5	7.7	1.83	90	2.05			
6	7.7	1.83	98	2.20			
7	7.7	1.83	95	2.19			
8	7.6	1.83	140	2.10			
9	7.5	1.83	125	2.48	.37	2.60	—.77
Average per day		1.83	112	2.23			

Period II

10	7.5	1.85	96	2.43	3.70	24.11	—5.79
11	7.4	1.83	110	2.22			
12	7.2	1.83	75	2.08			
13	7.3	1.83	85	2.14			
14	7.2	1.83	90	1.97			
15	7.3	1.83	85	1.90			
16	7.2	1.83	115	2.04			
17	7.2	1.83	90	1.93			
18	7.2	1.83	70	1.85			
19	7.2	1.83	75	1.85			
Average per day		1.83	89	2.04	.37	2.41	—.58

Period III

20	7.2	1.85	90	1.82	1.60	10.45	—1.28
21	7.1	1.83	75	1.70			
22	7.2	1.83	85	1.83			
23	7.2	1.83	82	1.73			
24	7.2	1.83	75	1.77			
Average per day		1.83	81	1.77	.32	2.09	—.26

TABLE III

*Dog I.**Diet Low in Nitrogen*

Casein (11.8%N.)	34.0	4.3 gm. N.
Sugar	35.0	
Lard	27.0	
Butter Fat	3.0	
Bone Ash	3.5	
Salt Mixture	2.0	520 Calories (estimated)
Dried Yeast (6.0%N.)	5.0	

Period I

Day	Body weight kgm.	Nitrogen intake gm.	URINE		Feces Nitrogen gm.	Total N. output gm.	Nitrogen Balance gm.
			vol. c.c.	Nitrogen gm.			
1	7.2	4.32	200	4.43	3.26	40.29	—1.57
2	7.3	4.30	190	4.00			
3	7.3	4.30	215	3.90			
4	7.2	4.30	200	3.92			
5	7.2	4.30	190	4.12			
6	7.2	4.30	200	4.09			
7	7.2	4.30	360	3.97			
8	7.2	4.30	270	4.22			
9	7.2	4.30	240	4.38			
Average per day		4.30	229	4.11	.36	4.48	— .18

Period II

10	7.2	4.32	140	4.03	1.37	18.81	—1.59
11	7.2	4.30	150	4.41			
12	7.1	4.30	150	4.41			
13	7.0	4.30	160	4.59			
Average per day		4.30	150	4.36	.34	4.70	— .40

Period III

18	7.2	4.32	150	3.61	2.30	21.08	+.44
19	7.2	4.30	220	3.70			
20	7.2	4.30	150	3.86			
21	7.2	4.30	210	3.79			
22	7.1	4.30	310	3.82			
Average per day		4.30	208	3.76	.46	4.21	+.09

TABLE IV

*Dog II.**Diet High in Nitrogen*

Casein (11.8%N.)	70.0	} 8.62 gm. N.
Sugar	35.0	
Lard	22.5	} 580 Calories (estimated)
Butter Fat	2.5	
Bone Ash	3.5	
Salt Mixture	2.0	
Dried Yeast (6.0%N.)	6.0	

Period I

Day	Body weight kgm.	Nitrogen intake gm.	URINE		Feces Nitrogen gm.	Total N. output gm.	Nitrogen Balance gm.
			vol. c.c.	Nitrogen gm.			
1	7.8	8.64	190	7.92	6.3	75.19	+2.41
2	7.8	8.62	170	7.62			
3	7.9	8.62	160	7.12			
4	7.8	8.62	175	7.55			
5	7.8	8.62	170	7.77			
6	7.8	8.62	150	7.42			
7	7.7	8.62	190	7.80			
8	7.8	8.62	160	7.77	0.7	8.35	+.27
9	7.7	8.62	160	7.92			
Average per day		8.62	169	7.65			

Period II

10	7.7	8.64	160	8.09	4.76	60.22	+.14
11	7.7	8.62	160	7.67			
12	7.7	8.62	160	8.07			
13	7.7	8.62	160	8.12			
14	7.7	8.62	160	8.07			
15	7.7	8.62	150	7.77			
16	7.7	8.62	190	7.67			
Average per day		8.62	163	7.92	0.68	8.60	+.02

Period III

17	7.7	8.64	160	8.65	3.66	51.24	+.50
18	7.7	8.62	160	7.92			
19	7.7	8.62	150	7.95			
20	7.7	8.62	150	7.77			
21	7.7	8.62	160	7.52			
22	7.6	8.62	155	7.77			
Average per day		8.62	156	7.92	0.61	8.54	+.08

TABLE V

*Dog III.**Diet High in Nitrogen*

Casein (12.3%N.)	73.1	9.36 gm. N.
Sugar	30.0	
Lard	27.0	
Butter Fat	3.0	
Bone Ash	3.5	
Salt Mixture	2.0	625 Calories (estimated)
Dried Yeast (6.0%N.)	6.0	

Period I

Day	Body weight kgm.	Nitrogen Intake gm.	URINE		Feces Nitrogen gm.	Total N. output gm.	Nitrogen Balance gm.
			vol. c.c.	Nitrogen gm.			
1	8.5	9.38	170	8.85	4.20	82.81	+1.45
2	8.6	9.36	150	8.65			
3	8.7	9.36	160	8.90			
4	8.7	9.36	160	8.70			
5	8.6	9.36	150	8.57			
6	8.7	9.36	150	8.67			
7	8.7	9.36	280	9.00			
8	8.7	9.36	170	8.50			
9	8.7	9.36	150	8.77			
Average per day		9.36	171	8.73	.47	9.20	+ .16

Period II

10	8.7	9.38	140	7.80	4.0	63.30	+2.24
11	8.7	9.36	155	8.51			
12	8.7	9.36	140	8.67			
13	8.7	9.36	140	8.77			
14	8.7	9.36	140	8.70			
15	8.8	9.36	150	8.65			
16	8.8	9.36	140	8.20			
Average per day		9.36	143	8.47	.57	9.04	+ .32

Period III

17	8.9	9.38	160	8.10	4.96	56.60	— .42
18	8.9	9.36	170	8.75			
19	8.9	9.36	170	8.97			
20	8.9	9.36	160	8.67			
21	8.9	9.36	155	8.45			
22	8.9	9.36	165	8.70			
Average per day		9.36	163	8.61	.82	9.43	— .07

TABLE VI

Tabular Summaries — Daily Averages

	Nitrogen intake gm.	Period	Nitrogen Balance gm.	Nitrogen utilization per cent
Dog I	1.60	1	— .15	92
		2	— .39	79
		3	— .42	79
Dog II	1.83	1	— .77	80
		2	— .58	80
		3	— .26	83
Dog I	4.30	1	— .18	92
		2	— .40	92
		3	+ .09	89
Dog II	8.62	1	+ .27	92
		2	+ .02	92
		3	+ .08	93
Dog III	9.36	1	+ .16	95
		2	+ .32	94
		3	— .07	91

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A TRIAL OF EUCALYPTUS INFUSION IN DIABETES.

By HENRY J. JOHN, M. D.

From The Physiatric Institute, Morristown, New Jersey

The first report of a beneficial influence of eucalyptus infusion upon diabetes was published by Dr. A. G. Faulds¹ in the Glasgow Medical Journal. Thereupon the following mention was made in the British Medical Journal².

"New remedies for diabetes are not uncommon, but none of them so far has stood the test of experience. Nevertheless a suggestion which we owe to the late Mr. James Dick, the Glasgow millionaire, and to Mr. A. G. Faulds of the Glasgow Royal Infirmary, is one which should be tried by those who have an opportunity of treating diabetic patients. The origin of the suggestion as told by Mr. Faulds is that some years ago Mr. Dick was traveling in New Zealand, and knowing that an old schoolmate of his was in the country, he determined to hunt him up. After considerable journeying he found his old friend, and a most agreeable interview followed. During this meeting the settler complained that his health had failed some years after he had settled in New Zealand and that the doctors had treated him for diabetes with but little effect. One day, however, having contracted a horrible cold or influenza, a neighboring old lady informed him that if he went to a certain eucalyptus tree, gathered some of the fresh leaves, and partook of an infusion of them two or three times daily, it would cure his influenza. The patient acted upon this advice at the earliest opportunity. He made an infusion of the fresh leaves and took a small teacupful night and morning, with the result that it not only cured his influenza but caused his diabetes also to vanish with all its symptoms. Mr. Faulds has endeavored to test this remedy in the following manner; he obtained some of the dried leaves of eucalyptus globulus, of which an infusion was made in a teapot by taking one teaspoonful of the broken leaves, about 60 grains in weight, and adding 6 oz. of water, letting it infuse for a half hour

and then adding a little saccharin. This quantity was given twice daily, and the remedy has been tried upon 46 cases, in 15 of which Mr. Faulds reports total disappearance of the disease, and so far as can yet be judged, a complete cure. The substitution of eucalyptus oil and eucalyptol was followed by no effect at all upon the sugar, and Mr. Faulds is unable to indicate to what constituent in the chemical composition of the infusion the therapeutic effect is due."

In March, 1920, the Bureau of Plant Industry of the U. S. Department of Agriculture transmitted to the Hygienic Laboratory of the Public Health Service a communication from Dr. George V. Perez, "La Quinta", Santa Ursula, Tenerife, from which the following is quoted:

"With regard to eucalyptus in diabetes, allow me to refer you to a letter of mine published in the Medical Press of London on the 21st of January last, page 52. * * * I hear from the Madeira botanist, St. Menezes, that in that island the patients suffering from diabetes, who have tried eucalyptus leaves, have all seen the quantity of sugar in their urine greatly reduced. In Madeira they tried the treatment after they heard of the favorable experiences in Tenerife. I again beg to refer you to my recent article, with an impartial summary of what has taken place and recommending its investigation in proper quarters as it should be done, as only then can the exact truth be ascertained."

In the above cited article of Perez³ favorable experiences with eucalyptus treatment in Algiers are narrated, the incentive there having come from an article in the *Revue Horticale de Algiers*. All varieties of eucalyptus are supposed to be active for the purpose, the common *Eucalyptus globulus* (blue gum) being suggested as possibly the best. A letter to an authority on eucalyptus in Sydney, N. S. W. elicited the information that the infusion or decoction had formerly enjoyed a considerable vogue there for diabetic treatment, but the benefits had not been substantiated by regular physicians and the usage had practically died out. Perez nevertheless gave his personal testimony of a beneficial influence on glycosuria and other symptoms in 400 diabetics using the remedy in Tenerife.

Trabut⁴ proposed to substitute eucalyptus for *Syzygium Jambolanum*, which was becoming difficult to obtain. He

calls attention to the fact that both are Myrtaceae. Dr. Perez, who had written to him that the eucalyptus treatment had abolished diabetes in Tenerife, had died recently. Trabut states that he invariably prescribes eucalyptus for his diabetic patients and has obtained marked benefits. He uses a decoction of 10 or 15 gm. of leaves in a liter of water, kept boiling till the volume is reduced to half.

This question was laid before the National Research Council at Washington, who in June, 1920, asked Dr. Frederick M. Allen to arrange for a trial of the proposed remedy. The writer therefore performed tests upon patients in the Physiatric Institute as described below.

PREPARATION OF INFUSION OR DECOCTION.

Eucalyptus globulus leaves from Golden Gate Park, San Francisco, were provided through the courtesy of Dr. G. W. McCoy, Director of the Hygienic Laboratory. Infusions were first made by taking 10 gm. of the air-dried leaves in 200 cc. water, bringing to boil, and filtering. Subsequently large quantities of fresh *Eucalyptus globulus* leaves were obtained from Southern California, and were used for making infusions and decoctions of various strengths. The freshness of the leaves, the quantity of them used, the duration of boiling, and other variations of preparation had no perceptible influence upon the clinical results.

RESULTS.

Two typical examples of the experiences are shown in detail in the charts.

Case No. 286. — This patient was a woman aged 55 years, with negative family history. She had been well except for minor infections up to 5 years ago, when polyuria was noticed and sugar discovered. Notwithstanding intermittent attempts at dieting, she has had heavy glycosuria most of the time since. She had been moderately obese at her ordinary weight of 165 pounds, but has gradually lost weight down to 90 pounds, and has also lost much strength, but is not confined to bed. Formerly three days of fasting always sufficed to abolish glycosuria, but since December, 1919, the glycosuria has resisted a week of continuous fasting, and her physician has feared to try any more extreme measures. She was once near coma, and had moderate acidosis at admission.

Treatment was begun with a diet limited to 40 gm. of protein and the small quantities of fat contained in the lean meat or fish used. This diet was made reasonably satisfying by the addition of bran, agar, and other bulky materials, as customary in this Institute. The heavy glycosuria of the day of admission (June 19) and the following day was not determined quantitatively. By June 25 the sugar excretion was somewhat reduced by the low diet, though the blood sugar was actually rising. On June 26 the blood sugar reached its highest level of 0.420 percent, while the urine became sugar free. On the next day glycosuria was still absent, the blood sugar had fallen slightly, and eucalyptus was begun with two doses of 50 cc. of the infusion. On the following day glycosuria reappeared and persisted notwithstanding increase of the dosage of the infusion to 600 cc. on July 2. The blood sugar and the glycosuria were both declining, however, as usual on such a low diet. The eucalyptus infusion was discontinued on July 4. Fasting was imposed from July 2 to 7 inclusive, followed by a diet of 10, 20 and 30 grams of protein respectively on July 8, 9 and 10. The blood sugar was thus brought to a minimum of 0.2 per cent, but then rose rather sharply on such a low diet as 30 gm. of protein.

The rise of sugar in the blood while the urinary excretion of sugar is diminishing is observed in some instances. The reappearance of glycosuria after its cessation on the same diet is rarer, but occurs sometimes when glycosuria has ceased with a very high level of blood sugar. The fall of weight on a low diet, followed by a rise on the same diet or on fasting, is a phenomenon of water retention in many patients during the treatment. None of these occurrences need be attributed to any special influence of the eucalyptus infusion either upon the diabetic process or upon the renal function. The entire therapeutic result was that which is familiar on the diet treatment alone.

Case No. 85. — Though the eucalyptus infusion had thus apparently failed to assist in clearing up a case with active symptoms, more accurate conditions were offered by a study of the food tolerance in a case under prolonged treatment. Patient No. 85 seemed ideal for this purpose. He was a young man of 30 years, with diabetes of 5 years duration. Notwithstanding almost continuous freedom from glycosuria, he had shown hyperglycemia accompanied by steady downward

progress from a mild to a severe stage of his disease. For some months before entering this Institute he had followed a nearly carbohydrate-free diet of 700 calories as the only means of preventing glycosuria. Upon admission he had been subjected to fasting and undernutrition to abolish his hyperglycemia, and the diet had then been built up gradually while keeping the blood sugar normal. He lived continuously in the Institute, and during a year his tolerance had slowly risen to 60 gm. protein, 3 gm. carbohydrate and 800 calories, with one fast-day each week on only 20 gm. protein. He then maintained an even weight and slightly improved strength, but every attempt to raise the diet more rapidly was checked by a rise of blood sugar. June 14, leaving the carbohydrate and protein portion of the diet unchanged, the fat was increased so as to make the total daily ration slightly over 1000 calories. The return of symptoms from the addition of fat alone was known not only from Dr. Allen's published experiments, but also from experiences with this individual patient. The blood sugar now rose steadily as expected, and by June 26 had reached a well-marked hyperglycemic level of 0.180 per cent. Eucalyptus infusion was then begun in dosage of 100 cc. daily, and as the blood sugar rose sharply and glycosuria appeared the dosage was increased to a maximum of 1700 cc. on June 30. The eucalyptus infusion was evidently unable to compensate for the slight increase of diet or for the omission of the weekly fast-day which had been due on June 27. To control symptoms and save injury to the patient, the diet was reduced radically from July 1 to 4. The sugar fell as usual, so the eucalyptus medication appeared at least to have no harmful influence. The infusion was discontinued on July 4. A lower diet and two partial fast-days were then necessary to restore the normal blood sugar.

The above fluctuation was not accidental or spontaneous, for the patient has continued more than a year since that time without disturbances and with a slowly rising tolerance. He is still a resident of the Institute, and has become able to assimilate a diet of 55 or 60 gm. protein, 10 gm. carbohydrate and 1100 to 1200 calories, with continuance of the normal blood sugar. It must, therefore, be concluded that the eucalyptus infusion had not the slightest effect in raising the tolerance, though the case was by no means hopeless and improvement was actually possible by means of dietary treatment.

General tests.—Quantities of eucalyptus leaves were obtained from Southern California as mentioned, and used partly in the moist state and partly in a dried condition for making infusions and decoctions, according to the directions of the authors mentioned and also with changes of various kinds. About 20 patients in the Institute received such infusions in various strengths over a period of two to three months. These patients represented a full range of types and stages of diabetes, from mild to severe at different ages, and each of them

drank from 1 to 3 liters of eucalyptus preparations per day. As there was not the slightest therapeutic effect, these observations need not be reported in detail. None of the aphrodisiac action reported by French authors was observed. There was also no sign of injury in the form of albuminuria, gastrointestinal disturbances or subjective feelings, and the use of the infusion was thus continued because the patients found it a pleasant drink. It seems to hold some possibilities as an occasional substitute for coffee, tea, or cocoa shells, but its use was finally allowed to lapse.

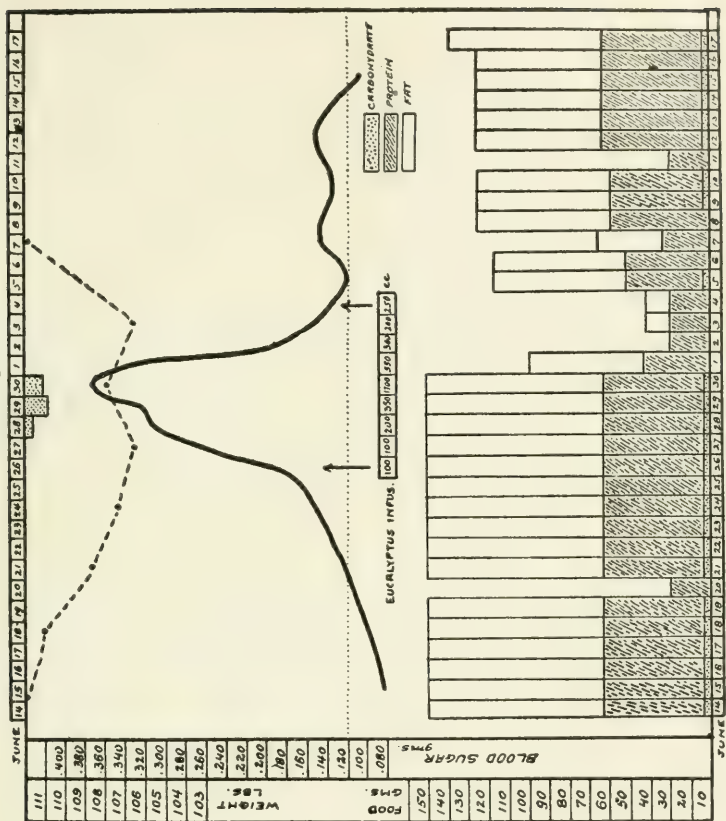
CONCLUSION.

The infusion of eucalyptus leaves has no influence upon diabetes. This fact could be predicted with fair certainty from existing knowledge of the pathology of this disease, but it is hoped that these negative observations under accurately controlled conditions will serve to overthrow the former claims of clinical benefits. It still stands as a fact that no drug has ever been found to possess any specific action upon diabetes.

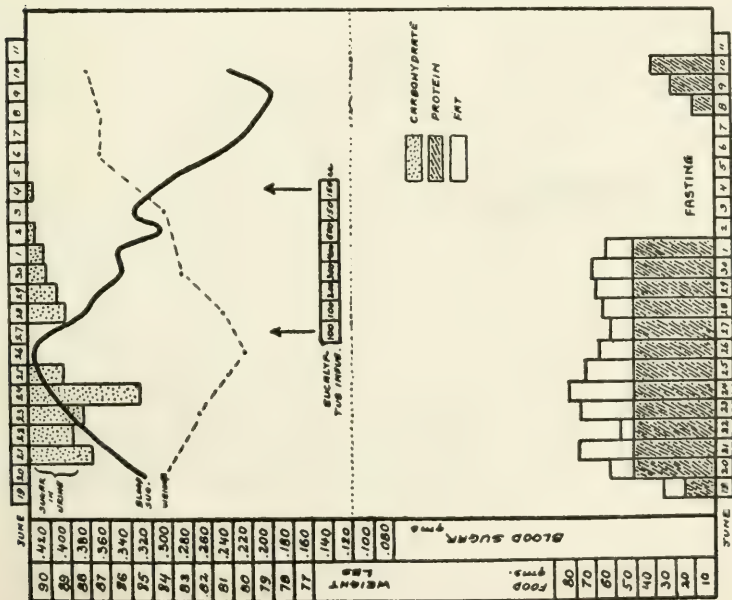
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CASE 85.



CASE 286.



GLUCOSE TOLERANCE AND ITS VALUE IN DIAGNOSIS.

BY HENRY J. JOHN, M. D.

From the Cleveland Clinic, Cleveland, Ohio.

The glucose tolerance test with parallel analyses of blood and urine seems to be the most delicate means of diagnosis of diabetes now available. At the same time, the recent widespread application of this method has disclosed abnormal curves of debated significance in a number of clinical disorders, particularly infections, obesity, hyperthyroidism, gastro-intestinal cancer, and certain types of renal and vascular disease.

Infections. Pemberton¹ cites cases of acute and of chronic tonsillitis with lowered glucose tolerance in which an increase of tolerance followed tonsillectomy. He reports other cases in which a rise of tolerance coincided with the subsidence of a chronic infection. He concludes that a lowered glucose tolerance is due to the presence of infection, hidden or obvious, and states that "our experience suggests that the sugar tolerance test may sometimes be helpful to indicate whether all foci have been removed". Assuming the correctness of this position, nevertheless, in view of the existing doctrine that diabetes is the result of infectious or toxic injury of the pancreas, the interpretation is permissible that these results indicate such pancreatic injury of various degrees of severity or permanency and therefore denote a true diabetic tendency.

Obesity. Paullin² made glucose tests in 26 cases of obesity without renal disorder. 5 of these patients showed a lowered tolerance, and of these, 2 later developed diabetes. Sherrill³ and others have also found lowering of the glucose tolerance in some but not all cases of obesity. It has long been known that a high proportion of obese persons sooner or later develop diabetes, and the importance of obesity among the causes of diabetes has recently been emphasized by Joslin⁴. It is supposed that the diabetes depends as usual upon pancreatic damage, and that the obesity places a strain upon the damaged organ. In any event there is little doubt that the lowered glucose tolerance of obesity can be interpreted as diabetic in character.

Hyperthyroidism. Boothby⁵ has recently stated that "the blood sugar curves following the ingestion of 100 gm. of glucose have not been sufficiently consistent in the different types of cases studied to be of diagnostic value, in spite of the fact that high and prolonged curves were more frequently found in patients with hyperthyroidism

than in those with hypothyroidism". Morris⁶ applied the glucose tolerance test in a series of borderline cases in which the diagnosis of hyperthyroidism was established by basal metabolism measurement. Comparisons were made with three normal individuals as controls. He found that (1) the cases of hyperthyroidism showed the highest rise of blood sugar in from 1½ to 2½ hours, while the normals showed the highest rise in one hour; and (2) the rise in the hyperthyroid cases was higher than in normals, and returned to normal after about 4 hours. He concluded that the test for alimentary hyperglycemia has distinct corroborative value in the diagnosis of mild hyperthyroidism. Janney and Isaacson⁷ found in animals after thyroidectomy an increased percentile rise of blood sugar in tolerance tests, but the absolute values were lower than normal, and the hyperglycemic curve was also delayed. In patients with hyperthyroidism the blood sugar was generally not above normal but delayed sugar curves were the rule. Geyelin⁸ concluded from a study of 27 cases of hyperthyroidism that an unmistakable hyperglycemia can be demonstrated in 90 per cent of the moderately severe cases. On the other hand, Denis, Aub and Minot⁹ have stated that "fasting hyperglycemia is of extremely rare occurrence in hyperthyroidism". In experimental work on animals, Hirsch¹⁰ showed that thyroparathyroidectomy lowers the assimilation limit for glucose, while with removal of the thyroid alone the tolerance is not lowered. The same fact has been demonstrated by Underhill and Saiki¹¹, Eppinger, Falta and Rudinger¹², and Pari¹³. Fitz¹⁴ considers that the intoxication and increased metabolism of hyperthyroidism may aggravate diabetes, even though not causing it, and thus relief of the thyroid disorder may result in improvement of the diabetes. The question must still be considered open whether thyroid intoxication directly disturbs the pancreatic function, whether in some cases of hyperthyroidism there is pancreatic damage independent of the thyroid disorder, and accordingly to what extent the abnormal glucose tests may be regarded as diabetic in character. Frank diabetes or marked lowering of assimilation with hyperthyroidism may certainly be regarded as due to pancreatic lesions, which should be sought for at autopsy. Olmstead and Gay¹⁵ found the hyperglycemic curves in hyperthyroidism to be high but steep, while diabetic hyperglycemia was generally both higher and more prolonged. Their findings with infections (furunculosis) and gastro-intestinal carcinoma confirmed those of the other authors here mentioned.

Gastro-intestinal Cancer. Freund¹⁶ in a series of 70 blood sugar determinations found hyperglycemia in patients with gastro-intestinal carcinoma but not with sarcoma. He therefore proposed blood sugar analyses for differential diagnosis between the two. Trinkler¹⁷, investigating a wide variety of diseases, found the highest blood sugar content in cases of carcinoma and regarded hyperglycemia as a constant accompaniment of carcinoma. Friedenwald¹⁸ has found hyperglycemia generally present in patients with gastro-intestinal carcinoma, even when fasting. After glucose ingestion, the blood sugar has risen as high as 240 mg. per 100 cc. within 45 minutes and remained above

200 mg. per 100 cc. for 2 hours or more. He has found the test valuable for the differential diagnosis between carcinoma and other diseases of the alimentary tract. These findings furnish an interesting contrast to the former belief that the pancreas may be almost entirely replaced by a carcinoma without diabetic manifestations. Pancreatic lesions should be looked for in the cases with lowered glucose assimilation. If absent, the hypothesis of toxic functional injury of the islands of Langerhans is open. There is reason to suspect that the lowering of tolerance in these cases is diabetic in character, because of the similarity of the curves to those of early diabetes.

Renal and vascular disease. — Hyperglycemia without glycosuria or clinical symptoms of diabetes has been reported by a number of authors in some cases of nephritis or arterial hypertension. A lowering of assimilation with the glucose tolerance test was demonstrated in such cases by O'Hare¹⁹, and by Sherrill²⁰. As numerous cases of nephritis, hypertension or arteriosclerosis display normal blood sugar and glucose tolerance, the impairment in some cases must be regarded not as a characteristic of the renal or vascular disease but as a complication. Such a complication is readily explained by the pancreatic arteriosclerosis and fibrosis of islands of Langerhans which are demonstrable in some cases of the above type, and which are presumably due to the same infectious or toxic causes which injured blood vessels in the kidney or elsewhere. This impairment of carbohydrate metabolism may therefore be regarded as diabetic or pre-diabetic in character, whether or not the clinical symptoms of frank diabetes are present.

The observations reported in the present paper were made upon patients in whom tolerance tests seemed indicated, and upon the writer and several assistants as normal controls. The indications for the tolerance test in patients were considered to be the following:

- 1) Glycosuria
- 2) Sudden obesity
- 3) Diabetes — chiefly to determine the severity of the condition and the renal permeability.
- 4) Hyperglycemia — as revealed by the routine blood sugar estimation.
- 5) The presence of fasting blood sugar to the amount of 125-135 mg. per 100 cc.; and of blood sugar 3 hours or more after a meal to an amount of 120 mg. or more mg. per 100 cc.
- 6) The familial occurrence of diabetes — to separate children who have the diabetic tendency from those who are normal.

Procedure. — The first blood specimen in each case was taken in the

morning before any food had been eaten, after which glucose was given as described below and no other food was permitted until the completion of the test. During the period of four or more hours required for the complete study, each patient remained in a private room where he was at liberty to sit up and read or to lie down as he chose.

Whenever it was possible, the patient was advised not to urinate in the morning until his arrival at the Clinic, in order that the urine might be secured just before the test. In any case the bladder was emptied before the first test was made. This accounts for the large urine output at the beginning of some of the studies. This amount, however, is not included in the calculation of the total output of urine during the period covered by the study, as this always started with an empty bladder. This initial specimen was used only as a control, to see whether or not the patient "started" with a glycosuria.

The first specimen of blood amounts to about 12-18 cc. in order to have a sufficient quantity for the determination of chlorides, urea, uric acid, creatinin, and for the Wasserman reaction, etc., in addition to the blood sugar estimation. From 6 to 8 cc. is taken for each of the subsequent tests.

Following the taking of the first specimen, the patient is given 100 gm. of anhydrous glucose dissolved in 250-350 cc. of water, to which the juice of one or two lemons is added. This solution is less nauseating if it is ice cold. The time is noted, and specimens of blood are taken at the end of the following periods — one-half hour, one hour, two, three and four hours. At the end of each hour the patient voids, each time in a separate jar, and is given 200 cc. of cold water to drink. The last water taken is not included in the total water intake, however, as no later specimen of blood is taken.

On each sample of blood the following observations are made:

- 1) Sugar content of whole blood; 2) Sugar content of plasma;
- 3) Sugar content of corpuscles; 4) Corpuscle volume; 5) A series of estimations of the sugar content by the Epstein method.

On each specimen of urine the following observations are made:

- 1) Total volume; 2) Specific gravity; 3) Presence or absence of sugar, qualitatively determined by the Benedict reagent; 4) Sugar content, quantitatively estimated by the Benedict method.

The blood sugar estimation is made by Myer's modification of Benedict's method, using the Kober colorimeter. The estimation of the corpuscle volume is made by centrifuging the oxalated blood at the rate of 3000 revolutions per minute for 10 minutes.

Explanation of charts. — The checkered columns at the top of the charts indicate the water intake; the solid black columns at the top indicate the urine output. The total intake and output during the period of four hours or more is indicated by a like marking at the lower right corner of the chart. The circles at the lower ends of the black columns indicate the presence of sugar in the urine.

The broken horizontal line opposite "120" is the upper limit of normal blood sugar, i.e., 120 mg. per 100 c.c. of blood. The broken vertical line

opposite "3 hours" is the period within which, in normal individuals, the blood sugar content again becomes normal after the ingestion of the standard dose of glucose. The heavy curve represents the blood sugar content at the designated periods. The dots which break the glucose tolerance curve indicate the intervals at which blood was taken for sugar estimation. Each solid black column at the bottom of the charts represents the sugar content of the urine output indicated by the corresponding solid black column at the top of the chart. Each square included in these lower columns represents one gram of sugar, and the total sugar output — the sum of these squares — is indicated by the solid black portion of the large square at the right of the chart, which includes 100 squares, representing 100 grams of glucose — the total sugar intake.

The detailed results in the entire series of 100 cases are here presented in the form of graphic charts, in the belief that only in this way can individual characteristics be displayed and the exact reactions of normal and abnormal individuals shown. These individual records are also to be used as a basis of comparison in future studies. The broader results of the investigation are grouped and summarized in a series of general tables and charts, and may be discussed as follows.

POINTS OF SPECIAL SIGNIFICANCE IN THE STUDY OF GLUCOSE TOLERANCE CURVES.

Relation of water intake to urine output.

It is generally conceived that diabetics put out large quantities of water. This is true in the early cases, but later on, after the burning thirst, which is a primary symptom, has subsided, a large urine output is not such a dominant factor. From Tables I and II, one can see that among the cases in our series the relation of the urine output to the water intake was as indicated in Table III.

The high percentage of diabetics showing a urine output less than the water intake can probably be explained on the basis that the hyperglycemia in the diabetic persists, and consequently the blood stream "holds" the water, whereas in the non-diabetic this happens to less extent. Among the non-diabetics about one-half readily eliminated the increased water intake, the other half withholding it to a considerable degree, the retention in some cases amounting to as much as 92.3 per cent of the water intake.

The accompanying charts (Charts I and II) show graphical-

ly the relation of the water intake to the urine output in the individual cases in our series.

PERIOD WITHIN WHICH HIGHEST RISE OF BLOOD SUGAR
CONTENT OCCURS.

That the rise of the blood sugar content after the ingestion of glucose is very prompt in normal individuals is clearly demonstrated by the accompanying curves (e.g., Charts 5, 8, 9, 10, 13, 17.) That the rise is markedly prolonged in the diabetics, the delay corresponding to the severity of the case, is also clear. (e.g., Charts, 6, 9, 71, 73, 74, 75.) This comparison is well demonstrated by the accompanying tables (Tables IV, V and VI).

As is shown by the graphic presentation of these percentages in Chart III, the two curves start in opposite directions, that of the non-diabetics falling promptly, while the diabetic curve rises just as promptly, the two intersecting shortly after one hour. While larger series may change the shape of these curves somewhat, their general course will remain the same.

Has the height of the blood sugar curve any significance? — The importance of a single high peak of blood sugar is doubtful. If there is a quick absorption, the blood stream is flooded and the curves rise higher than if this absorption is somewhat slower. I have found some very high rises in normal individuals (not included in this series). In these cases, however, the curve promptly returned to the normal level, so that I doubt whether the absolute height has much significance. The most important point would appear to be the length of time after the ingestion of sugar before the curve intersects the base line.

The importance of the blood sugar content at the end of the first one-half hour after the ingestion of glucose. — Were one to disregard this estimation, the highest rise of the curve in 50.8 per cent. of the non-diabetics and in 4.6 per cent. of the diabetics would be missed. A mere glance at the curves demonstrates this point clearly, and emphasizes the importance of making this early estimation in such a study as this. Nevertheless, for practical use, the half-hour estimation is of less importance for diagnostic purposes, the sugar content of the fasting and the three hour specimens being of most importance.

The Normal Standard. — Most investigators have accepted

as a normal standard the curve which returns to normal within three hours; i.e., in the normal individual the blood sugar returns to the normal level within three hours after the ingestion of 100 gm. of glucose. We might be more exacting and accept a two and one-half or even a two hour limit, but that would be a somewhat too rigid rule, for thus we might be classifying other types of lowered tolerance as diabetic. The variations of individual cases within this three hour zone are discussed elsewhere. It should be added, however, that a slight over-stepping of this three hour period also must be interpreted with caution, for, as other investigations have shown, the fall of the blood sugar curve may be slightly delayed under other conditions than diabetes. One should never lose sight of the clinical aspect of his cases and should use glucose tolerance as an aid to diagnosis, rather than as an absolute diagnostic measure.

Is a Delayed Rise of Blood Sugar Due to Lack of Absorption in the Intestine? — This question has been raised a number of times. Should this be a serious factor, the rise would be delayed in many non-diabetic individuals with gastro-intestinal disturbances. This, however, is not the case. Invariably in the non-diabetic, the rise is prompt, the peak being reached in from one-half to one hour. This must mean that absorption is prompt, that the sugar enters at once into the circulation, from which it is promptly utilized. The curves of the diabetics also rise rapidly, but they continue to climb, since the body cannot store or utilize the sugar fully. The organism attempts to excrete it, but as we can see, this process of excretion is slow in the great majority of individuals.

The Effect of Nausea on the Glucose Tolerance Curves. — The peculiar "dips" in the following curves, in No. 15 at $\frac{1}{2}$ hour, in No. 20 at 1 hour, in No. 25 at 1 hour, in No. 27 at 1 hour, in No. 40 at 1 hour, in No. 63 at $\frac{1}{2}$ hour, in No. 88 at 1 hour, in No. 91 at 2 hours, and in No. 96 at 1 hour, are due to nausea. These curves indicate that if a patient is nauseated, absorption is delayed or stopped for a short time. For this reason it is useful and necessary to add the juice of one or two lemons to the glucose. After experimenting with many ways of obviating this nausea, we have found that the best method is to keep the glucose solution on ice over night and add the lemon juice to it before ingestion.

THE RENAL THRESHOLD.

The sugar threshold of the kidney is known to vary widely. Jacobsen²¹ studied the alimentary hyperglycemia after the intake of glucose in 13 adults. He found that when the alimentary hyperglycemia was below 160 mg. per 100 cc. there was no sugar in the urine; while with hyperglycemia above 170 mg. per 100 cc. sugar appeared. Von Noorden²² states that in one case of pneumonia the level of the blood sugar was 280 mg. per 100 cc. and there was no sugar in the urine. Graham²³ cites two cases in which the blood sugar content was 280 and 260 mg. per 100 cc. without sugar in the urine. MacLean and De Wesselow²⁴ do not consider that glycosuria in itself is evidence of hyperglycemia unless the renal threshold is known. Sherrill and John²⁵ cite the case of a very severe diabetic with blood sugar 256 mg. per 100 cc. and no sugar in the urine. Hamman and Hirschman²⁶ investigated the renal threshold in six normal individuals and found that the threshold was lowered in some of them. They state that "The renal threshold is not constant in every normal person and it is often low."

Goto and Kuno²⁷ gave 50 gm. of glucose to a group of persons in whom glycosuria had appeared after the ingestion of 100 gm. of glucose. Glycosuria appeared in five out of fourteen of these. They found that 33 among 53 healthy Japanese adults — 62 per cent. — eliminated sugar in the urine after the ingestion of 100 gm. of glucose, although the quantity eliminated was very small. They found the morning blood sugar in normal adults to lie between 66 and 166 mg. per 100 cc. In the eight cases referred to above the normal thresholds were as follows: 122-129 mg. per 100 cc., 120-122 mg. per 100 cc., 123-135 mg. per 100 cc., 139 mg. per 100 cc., 142-160 mg. per 100 cc., 146 mg. per 100 cc., 160 mg. per 100 cc.

My own findings regarding the presence or absence of glycosuria in the presence of a high blood sugar content are shown in the appended table and charts (Tables VII to XII, Charts IV to VIII) which are based on 714 observations. In these tables I have included all my observations on this point up to this time, in order to base conclusions on as large a series as possible. These observations cannot be offered as final criteria. Thus, if glycosuria appears with a blood sugar content of

180 mg. per 100 cc., it follows that if the blood sugar curve continues to rise and remains high the glycosuria will continue and the later observations will be classed with the higher glycemia. There is, however, some value in an analysis of this sort, in view of the number of cases of normal glycemia with glycosuria and those of hyperglycemia without glycosuria. In this series of 715 observations (Table VII), in 99, i.e., 13.8 per cent., glycosuria occurred in the presence of a normal blood sugar, while in 131 (18.3 per cent.) glycosuria was not manifested in the presence of hyperglycemia. That is, 32.1 per cent. of our total series ran contrary to the generally accepted rule. This percentage is much higher than is ordinarily reported in the literature when a small series is considered. It shows the importance of making large series of blood sugar estimations in order to establish this point. If 13.8 per cent. of cases with normal blood sugar show glycosuria, many normal patients will be treated as diabetics if one uses the urine examinations as the sole criterion. On the other hand, if 18.3 per cent. of cases of hyperglycemia do not show glycosuria, many cases of diabetes must be missed when only a urine examination is made. Thus, the percentage of error in diagnosis when a urine examination alone is made may be 32.1 per cent., if my series represents a fair average.

The accompanying curves show also that the progress of but few diabetics can be judged by urine examinations alone. The urine examination provides a fair criterion only when the renal permeability is at about 120 mg. per 100 cc. This happens in only the exceptional case, the permeability being usually at a high level, although, as we have stated, a sieve-like renal filter is present in a few cases.

It follows from these premises that there is no such thing as a "normal renal threshold". One might substitute, therefore, the term "individual threshold", which varies with each individual. The "individual threshold" is the normal upon which our interpretations and our conclusions in that individual case should be based. In some cases the "individual threshold" is high; in others it is low; always it is a law unto itself. It is a well known fact that in cases of untreated diabetes the renal threshold is raised. Macleod²⁸ says "The toxic effect of high blood sugar renders the kidneys impermeable

to it." This may perhaps be the case also when the renal filter is damaged by some kidney affection.

Hamman and Hirschman²⁶ have concluded from their studies that diabetics have a lowered renal threshold excepting in the presence of nephritis. My figures do not bear out this conclusion. The renal threshold of non-diabetics is ordinarily considered to be at 170 mg. per 100 cc. However, an examination of the accompanying table shows that in our series in the non-diabetics the renal threshold was below this point in 34 cases as compared with 12 diabetics; while we find a renal threshold about 175 mg. per 100 cc. in only one non-diabetic as compared with 12 diabetics. Thus, it would appear that the renal threshold in diabetics is definitely raised, and our observations indicate also that the more protracted and severe the case of diabetes the higher the threshold. This agrees fully with the observations of Macleod. Locke and Ohler²⁹ have reported very interesting observations in this connection, namely, two patients, who on first examination reacted in the manner of renal glycosuria (slight glycosuria after glucose ingestion with blood sugar constantly below 0.1%) have shown changes after respectively one and two years of observation, so that both of them now react to the glucose test with definite hyperglycemia in addition to glycosuria. Doubt is thus cast upon the infallibility of the glucose test and blood sugar analyses for a differential diagnosis between renal glycosuria and true diabetes.

THE EFFECT OF RESTRICTION OF CARBOHYDRATES UPON THE GLUCOSE TOLERANCE.

A study of curve 54 shows that while the fasting blood sugar was only 90 mg. per 100 cc., nevertheless, after the ingestion of glucose, the normal level was not reached for three hours. During this period each urine examination with the exception of the last showed glycosuria; the urine output was low as compared with the water intake. This curve is that of a young college student, 20 years old, in apparently good health. Later the subject himself explained this condition by telling me that during the entire school year he had been eating large amounts of sweets and pastries. The delayed fall of the blood sugar curve led me to prescribe a diet with restricted carbo-

hydrates, to which he adhered during the summer vacations, during which time he worked on a farm. At the end of the vacation another glucose tolerance test was made (Curve 102) which shows a marked contrast to the first in the prompt fall of the curve after the initial rise; moreover, at this later time, there was no glycosuria.

Curve 100 is that of a severely diabetic patient, a street-car conductor, 32 years of age. The diabetes had come on suddenly, only three weeks before this test was made; but in spite of its short duration, he was in a markedly toxic condition. As is shown by the typical diabetic curve, the rise and fall of the blood sugar was prolonged, and he had a marked glycosuria. A rigid routine was prescribed to which the patient responded promptly, for his blood sugar became normal within three days. He remained in the hospital for three weeks, and was discharged on a diet of 75 gm. protein, 75 gm. carbohydrate and 1700 calories, which he assimilated well. Another glucose tolerance test was made when he was discharged (Curve 103). The contrast to the first curve (100) is noteworthy; the highest rise is at the end of the second hour, and while the curve still is characteristic of diabetes, the return to the normal level is more prompt than at first.

The tolerance curves of these two cases, one an apparently normal individual, the other a diabetic of severe type, offer sufficient evidence of the effect of restriction of carbohydrates upon the blood sugar content and assimilative capacity.

WASSERMANN REACTION

The Wassermann test with three separate antigens was made in 91 of the 100 cases in this series, with positive reactions in only two of the cases — 2.19 per cent.

Rosenbloom³⁰ states that the Wassermann reaction was positive in 12 per cent. of his series of 139 cases of diabetes mellitus. He considers that the arteriosclerosis of diabetes is due to syphilis and not to diabetes.

Mason³¹ obtained strongly positive reactions in cases of diabetes mellitus in which there was no history of infection. These cases cleared quickly upon treatment. He thinks that the Wassermann reaction in diabetes must be interpreted conservatively.

Joslin³², also Williams³³, find syphilis comparatively rare with diabetes.

THE COMPARATIVE VALUE OF DIFFERENT METHODS OF BLOOD SUGAR ESTIMATION.

The figures in Table XIII are offered to show the accuracy of the Epstein blood sugar method as compared with the standard technic. In the former, too many small factors disturb accurate control and the results are correspondingly unreliable.

RELATIVE BLOOD VOLUME.

Only relative blood volume studies have been made, these being based on the corpuscle volume of the first blood taken, i.e., before glucose is ingested. This volume is used as a basis of comparison for the subsequent examinations. The relative percentile increase or decrease of blood of the individual case, therefore, is based on this initial volume in that case. As an extreme example, if the corpuscle volume is estimated as 50 per cent., and at the end of one hour is 25 per cent., we conclude that the plasma volume has increased from 50 to 75 per cent., i.e., has increased to 150 per cent. of its original volume. It is on this basis that the appended tables have been calculated. (Tables XIII-XV).

There seems to be no general distinction between the changes in blood volume in the diabetic and in the non-diabetic. (Tables XVII and XVIII). The essential points appear to be the concentration of the blood sugar and the increase or decrease in the urinary output, whether this be in a diabetic or a normal individual. Changes in the blood volume appear to be related to the output of urine.

SUMMARY.

1. The urine output during the period of observation was greater than the water intake in 25.5 per cent. of the diabetics and 42 per cent. of the non-diabetics; the urine output was smaller than the water intake in 74.5 per cent. of the diabetics and 50 per cent. of the non-diabetics. As there is no fixed limit

between the diabetic and non-diabetic state, but rather all degrees of transition from the normal to the severest diabetes, these data are difficult to interpret.

2. The rise of blood sugar in the non-diabetics appeared very promptly after the ingestion of glucose, in 50.9 per cent. in one-half hour and in 36.8 per cent. in one hour. These facts are believed to exclude delayed absorption as a serious disturbing factor. In the diabetics this rise was slow, as was also the return to the normal level. In only 4.6 per cent. the highest rise appeared one-half hour after the ingestion of glucose; in 32.5 per cent. it appeared at the end of one hour; in 49 per cent. at the end of two hours — in the rest at still later periods.

3. Altogether the highest rise of blood sugar was reached at the end of one-half hour in 55.4 per cent. of the cases. The mere peak of the blood sugar content after the ingestion of glucose appears to have little or no significance. The most important point is the length of time which it takes for the re-establishment of the normal level. After the ingestion of 100 gm. glucose, if the curve comes back to normal inside of three hours, the individual is considered non-diabetic; if after three hours, he is considered diabetic.

4. While final evidence cannot be offered to prove that a delayed rise in the blood sugar content is not due to lack of absorption from the intestine, it seems more probable that a deficiency of storage, utilization and excretion protracts the rise.

5. Nausea produces a temporary lack of absorption from the stomach which is characterized by a 'dip' in the curve.

6. Glycosuria and hyperglycemia are two independent factors, either of which may be present alone, or they may be co-existent. The significance of glycosuria can not be determined without simultaneous blood sugar estimation.

7. There is no such thing as a fixed "normal renal threshold" (usually placed at 170 mg. per 100 c.c.) for all individuals. Every individual is a law unto himself and may have either a high or a low renal threshold, an "individual threshold", which is normal for the individual in question. This threshold changes in cases of untreated diabetes and perhaps in nephritic cases also.

8. Restriction of carbohydrates improves the tolerance (lowers the curve) in diabetics and in pre-diabetics.

9. The micro-methods for blood sugar estimations are less reliable than the standard method.

10. In this series of 100 cases, only 2.19 per cent. showed a positive Wassermann reaction.

CONCLUSION.

The sugar analyses of blood and urine in a series of varied cases show gradations of assimilation which may be designated as (1) strong normal, (2) normal, (3) weak normal or pre-diabetic, (4) diabetic. With all possible allowances for uncertainties presented by renal glycosuria, toxic or infectious states, or other endocrine disorders, the simple glucose test undoubtedly reveals an important number of cases of early or latent diabetes, in which prophylactic dietary regulation is a rational procedure. Studies of the largest possible numbers of such cases over the longest possible period of time will be necessary to establish their progress with certainty, but it seems probable that many cases of diabetes may be prevented by diet instituted on the basis of glucose tolerance tests in the pre-diabetic stage.

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TABLE I.

*The relation of the water intake to the urine output.
Non-Diabetic.*

No.	Intake	Output	%Incr.	%Decr.	Hrs.	No.	Intake	Output	%Incr.	%Decr.	Hrs.
1	900	1360	50.5	—	4	29	900	910	7	—	4
2	1100	295	—	73	5	30	850	610	—	28.2	5
3	900	379	—	57.8	4	31	850	650	—	23.5	4
4	900	1180	31.2	—	4	32	700	335	—	52.5	3
5	1100	1052	—	5	5	33	850	920	8	—	4
6	900	162	—	82.1	4	34	850	1140	34.1	—	4
7	850	460	—	45.8	4	35	900	1105	22.2	—	4
8	900	860	—	4	4	36	850	1800	11.3	—	4
9	850	534	—	37.2	4	37	850	570	—	33	4
10	850	1710	10.1	—	4	38	900	1220	35.5	—	4
11	850	325	—	61.6	4	39	900	1170	31	—	5
12	850	820	—	3.5	4	40	900	659	—	27.2	4
13	900	1060	18.6	—	4	41	850	1102	30	—	4
14	900	170	—	81.2	4	42	850	280	—	67	4
15	900	1015	12.2	—	4	43	850	690	—	19.7	4
16	950	74	—	92.3	4	44	850	1418	48.4	—	4
17	1050	194	—	81.6	5	45	850	495	—	41.7	4
18	900	695	—	11.2	4	46	900	468	—	48	4
19	925	203	—	28	4	47	850	1020	22	—	4
20	900	1239	37.2	—	4	48	850	890	4.5	—	4
21	850	850	0	0	4	49	700	1290	83	—	3
22	900	220	—	75.5	4	50	850	363	—	57.5	4
23	900	255	—	71.5	4	51	850	1485	73	—	4
24	850	285	—	66.5	4	52	850	1300	52	—	4
25	850	1165	25	—	4	53	900	1350	50	—	4
26	850	478	—	44	4	54	850	194	—	77.2	4
27	850	1250	46.5	—	4	55	1100	1140	2	—	5
28	850	285	—	66.5	4	58	1100	940	—	14.9	5
						60	850	334	—	60.8	4

Total number of cases 57

Total number where the output is increased 24, percent 42.

Total number where the output is decreased 33, percent 58.

TABLE II.

*The relation of the water intake to the urine output.
Diabetic.*

No.	Intake	Output	%Incr.	%Decr.	Hrs.	No	Intake	Output	%Incr.	%Decr.	Hrs.
56	850	675	—	20.8	4	81	850	1188	40	—	4
57	1150	906	—	21.5	6	82	850	818	—	15.8	4
59	900	570	—	36.8	4	83	850	575	—	32.5	4
61	850	510	—	40.0	4	84	900	1075	19	—	4
62	1100	1430	30.0	—	5	85	850	555	—	35	4
63	900	1264	41	—	4	86	850	905	6.4	—	4
64	900	1665	85	—	4	87	850	850	0	0	4
65	900	430	—	52.2	4	88	850	925	8.8	—	4
66	900	400	—	51.4	4	89	850	530	—	37.5	4
67	900	1245	39	—	4	90	850	855	0	0	4
68	850	501	—	50.6	4	91	850	860	1.1	—	4
69	1100	1010	—	9	5	92	850	655	—	23	4
70	1100	1000	—	8.5	5	93	850	310	—	63.5	4
71	1300	870	—	33.4	6	94	650	390	—	40	3
72	900	561	—	37.7	4	95	1100	614	—	44.4	5
73	700	650	—	7	4	96	850	690	—	19.7	4
74	900	320	—	64.5	4	97	1100	800	—	27.4	5
75	900	366	—	59.4	4	98	1500	1390	—	7.4	7
76	900	690	—	23	4	99	1050	1475	40	—	5
77	1100	1405	28	—	5	100	1050	912	—	9.5	4
78	850	537	—	37	4						
79	850	341	—	60	4						
80	1100	935	—	15.5	5						

Total number of cases 43.

Total number where the output is increased 11, percent 25.5

Total number where the output is decreased 32, percent 74.5

TABLE III.

Relation of the Water Intake to the Urine Output.

Diabetics

Non-Diabetics

	(Total No. of cases—57)	(Total No. of cases—43)
Urine output greater than water intake.	25.5 per cent.	42 per cent.
Urine output less than water intake.	74.5 per cent.	58 per cent.

TABLE IV.
Highest rise of blood sugar content.
Non-Diabetic.

No.	$\frac{1}{2}$ Hour	1 Hour	2 Hours	3 Hours
23	173	—	—	—
40	194	—	—	—
49	—	234	—	—
58	—	280	—	—
38	209	—	—	—
13	—	—	—	143
39	—	222	—	—
2	124	—	—	—
5	148	—	—	—
3	117	—	—	—
15	—	143	—	—
32	—	145	—	—
14	151	—	—	—
4	124	—	—	—
18	174	—	—	—
19	—	149	—	—
17	162	—	—	—
22	124	—	—	—
54	—	—	—	—
44	196	—	195	—
55	—	—	—	—
16	—	141	230	—
46	—	191	—	—
6	—	136	—	—
53	—	—	—	—
24	207	—	250	—
9	160	—	—	—
33	212	—	—	—
48	—	—	—	—
8	155	—	178	—
20	—	—	—	—
45	—	—	147	—
36	183	102	—	—
1	—	—	—	—
29	163	—	—	—
10	135	—	—	—
35	163	188	—	—
52	—	177	—	—
37	—	—	—	—
27	—	159	—	—
51	—	228	149	—
28	—	185	—	—
7	148	—	—	—
31	167	—	—	—
30	—	175	—	—
11	158	—	—	—
12	156	—	—	—
34	163	—	—	—
43	—	202	—	—
60	—	420	—	—
26	—	174	—	—
47	256	—	—	—
42	183	—	—	—
21	207	—	—	—
41	—	156	—	—
50	—	—	—	—
25	158	230	—	—
Total 57	29	21	6	1
Percent	50.8	36.8	10.5	1.7

TABLE V.
Highest rise of blood sugar content.
Diabetic.

No.	$\frac{1}{2}$ Hour	1 Hour	2 Hours	3 Hours
66	—	329	—	—
64	—	329	—	—
65	212	—	—	—
62	—	227	—	—
71	—	240	—	—
98	—	—	467	—
97	—	—	—	428
67	—	—	348	—
89	—	370	—	—
69	—	—	267	—
73	—	—	213	—
59	—	240	—	—
95	—	—	398	—
57	—	—	176	—
68	—	—	254	—
70	—	—	305	—
63	—	187	—	—
72	—	256	—	—
74	—	—	334	—
76	—	—	309	—
75	—	—	300	—
77	—	333	—	—
99	—	—	645	—
87	—	—	425	—
96	—	—	425	—
94	—	—	—	359
93	—	—	330	—
92	—	—	—	308
86	—	510	—	—
91	—	—	—	379
88	368	—	—	—
83	—	—	—	405
89	—	—	—	557
84	—	—	420	—
85	—	—	485	—
100	—	—	636	—
56	—	—	205	—
83	—	—	411	—
90	—	—	522	—
78	—	460	—	—
81	—	374	—	—
79	—	352	—	—
Total	43	14	21	6
Percent . .	4.6	32.6	49	13.9

TABLE VI.

Comparison of Highest Rise of Blood Sugar Content after Ingestion of Glucose in Diabetes and in Non-Diabetics.

Highest rise of blood sugar	<i>Non-Diabetics</i> Total number of cases — 57.	<i>Diabetics</i> Total number of cases — 43.
at end of $\frac{1}{2}$ hour	in 50.9 per cent.	in 4.6 per cent.
“ “ “ 1 hour	“ 36.8 “ “	“ 32.5 “ “
“ “ “ 2 hours	“ 10.5 “ “	“ 49. “ “
“ “ “ 3 hours	“ 1.8 “ “	“ 13.9 “ “

TABLE VIII.

Renal Threshold.

mgm/100 cc	50 75	75 100	100 125	125 150	150 175	175 200	200 225	225 250	250 300	300 up
Non-Diabetics . . .	5	14	8	4	3	—	1	—	—	—
Diabetics	—	1	4	4	3	8	4	1	8	6

NOTE:—The rest of the series of 100 started with a glycosuria and consequently the renal threshold could not be determined.

TABLE VII
THE RENAL THRESHOLD

mgm/100 c. c.	Number of Cases																									
	40 50	50 60	60 70	70 80	80 90	90 100	100 110	110 120	120 130	130 140	140 150	150 160	160 170	170 180	180 190	190 200	200 210	210 220	220 230	230 240	240 250	250 300	300 350	350 up		
1	6	4	20	14	17	22	15	Normal Glycemia with Glycosuria.																		
4	12	21	35	35	37	48	36	9	12	14	12	8	16	8	9	11	6	5	7	6	27	35	71			
																									Hyperglycemia without Glycosuria.	
Hyperglycemia without Glycosuria.																										
.....	29	21	15	15	9	10	3	4	7	2	1	6	1	3	2	3	

This is based on 714 observations.

TABLE IX.
Percentage of Excretion of sugar at different hour periods.
Non-Diabetic

No.	Total Hours.	Gms. Total Sugar	Gms. 1 Hr.	Per Cent	Gms. 2 Hrs.	Per Cent.	Gms. 3 Hrs.	Per Cent.	Gms. 4 Hrs.	Per Cent.	Gms. 5 Hrs.	Per Cent.	Gms. 6 Hrs.	Per Cent.	Gms. 7 Hrs.	Per Cent.
3	3	.207	.0136	6.5	.0635	31.5	.0395	19.6	.0882	44	—	—	—	—	—	—
5	1	.271	.0742	27.4	.073	27.4	.0878	32.6	.0332	12.4	—	—	—	—	—	—
6	4	.77	.13	16.9	.13	16.9	.37	48	.14	18.1	—	—	—	—	—	—
7	4	.208	.052	25	.057	26.4	.032	15.3	.067	32	—	—	—	—	—	—
14	4	.360	.0720	20	.073	20.5	.0099	2.5	.206	57	—	—	—	—	—	—
15	2	1.228	.957	78	.209	17	.062	5	—	—	—	—	—	—	—	—
16	4	.103	.0468	46	.0195	17	.0174	16	.0197	19	—	—	—	—	—	—
17	5	.035	.0073	21	.014	40	.0069	18	.0041	10	.0046	11	—	—	—	—
18	2	.5	.25	50	.25	50	—	—	—	—	—	—	—	—	—	—
19	3	.374	.084	22.4	—	—	.04	17	.25	67	—	—	—	—	—	—
22	3	.114	.07	61	.0217	19	.023	20	—	—	—	—	—	—	—	—
26	1.5	.058	.058	100	—	—	.06	14.7	.054	13.5	—	—	—	—	—	—
27	4	.408	.256	62.5	.038	9.3	—	—	—	—	—	—	—	—	—	—
39	2	.96	.37	38.9	.59	61.5	—	—	—	—	—	—	—	—	—	—
40	4	1.687	.460	28.5	.219	13	.786	46.5	.222	13	—	—	—	—	—	—
45	4	.145	.0077	4.6	.064	44	.050	34.4	.025	17	—	—	—	—	—	—
46	2	.062	.031	50	.031	50	—	—	—	—	—	—	—	—	—	—
49	3	.050	.014	28	.027	54	.009	18	—	—	—	—	—	—	—	—
50	2	.233	.13	55.8	.10	44.2	—	—	—	—	—	—	—	—	—	—
51	3	1.87	.22	11.8	1.33	71	.32	17.2	—	—	—	—	—	—	—	—
54	3	.268	.066	24.6	.132	49	.032	12	.038	14.4	—	—	—	—	—	—
55	5	.342	.084	24.5	.13	38	.072	21	.03	8.8	.026	7.7	—	—	—	—
58	5	52.32	7.42	14	37.5	72	5.2	10	—	—	2.2	4.4	—	—	—	—
60	2	1.00	.44	44	.56	56	—	—	—	—	—	—	—	—	—	—
TOTAL				860		830.7		367.8		326.2		22.7				

TABLE X.
Percentage of Excretion of sugar at different hour periods.
Diabetic

No.	Total Hours	Gms. Total Sugar	Gms. 1 Hr.	Per Cent.	Gms. 2 Hrs.	Per Cent.	Gms. 3 Hrs.	Per Cent.	Gms. 4 Hrs.	Per Cent.	Gms. 5 Hrs.	Per Cent.	Gms. 6 Hrs.	Per Cent.	Gms. 7 Hrs.	Per Cent.
63	3	.043	.012	28.1	.018	42	.013	30	—	22	—	—	—	—	—	—
64	4	.877	.036	4.0	.505	58	.144	16	.192	18	—	—	—	—	—	—
66	4	.69	.26	37	.27	29	.04	6	.12	50	—	—	—	—	—	—
68	4	3.21	1.04	32	.51	16	.07	2	1.59	1	.324	7	—	—	—	—
69	5	4.678	.055	1	2.02	44	2.25	47	.054	21	1.4	19	—	—	—	—
70	5	7.51	.715	9	1.4	19	2.4	32	1.6	14	.134	11	.142	—	—	—
71	6	1.279	.162	12	.451	35	.202	16	.188	14	—	—	—	—	—	—
73	4	1.25	.058	4	.065	5	—	—	1.13	91	—	—	—	—	—	—
79	4	3.04	0.2	7	.645	22	1.44	46	.76	25	2.16	6	—	—	—	—
80	5	41.53	1.92	5	9.36	22	13.34	32	14.75	35	—	—	—	—	—	—
81	3	4.54	.62	14	1.96	43	1.96	43	—	5	—	—	—	—	—	—
82	4	5.56	1	18	2.80	50	1.47	27	.29	—	—	—	—	—	—	—
83	3	11.84	1.44	12	4.16	35	6.24	53	—	—	—	—	—	—	—	—
84	3	10.86	1.69	15	6.12	56	3.05	29	—	—	—	—	—	—	—	—
85	4	19.90	1.32	13	8.07	38	7.59	35	2.92	14	—	—	—	—	—	—
86	4	50.25	8.43	17	22.05	44	19.14	38	.63	1	—	—	—	—	—	—
87	4	17.62	3.12	17	5	29	8	46	1.5	8	—	—	—	—	—	—
88	4	19.24	2.9	15	7.22	38	6.65	34	2.47	13	.88	10	—	—	—	—
89	5	8.46	.43	5	3.03	35	4.12	50	4.51	14	—	—	—	—	—	—
90	4	32.53	8.7	27	11.8	36	7.52	23	4.51	14	—	—	—	—	—	—
91	4	3.96	.92	23	1.59	40	1.59	40	1.45	37	—	—	—	—	—	—
92	4	6.03	1.19	30	1.19	30	3.36	56	1.48	24	—	—	—	—	—	—
93	4	4.55	.75	17	.75	17	1.87	41	1.02	22	—	—	—	—	—	—
94	3	5.06	.84	17	1.95	39	2.27	44	—	—	—	—	—	—	—	—
96	4	17.24	3.75	22	4.5	26	6.12	35	2.87	17	—	—	—	—	—	—
97	5	.845	—	5	3.1	18	5	30	5.62	34	2.17	13	—	—	—	—
98	7	13.16	1.56	11	1.57	12	1.71	13	1.78	14	1.73	14	1.69	12	1.60	12
100	4	59.72	11.05	19	19.99	33	16.92	28	11.76	20	—	—	—	—	—	—
TOTAL				376.1		894		792		500		80		24		12

TABLE XI.
Total excretion of sugar.
(Intake 100 gms.)
Non-Diabetic.

No.	Hours	Sugar Gms.	Per cent. Exc.
3	3	.207	.2
5	1	.267	.2
6	4	.77	.7
7	4	.208	.2
14	4	.206	.2
15	2	1.297	1.2
16	4	.103	.1
17	5	.037	.03
18	2	.50	.5
19	3	.375	.37
22	3	.114	.11
26	1.5	.058	.05
27	4	.308	.3
37	2	.287	.28
39	2	.962	.96
40	4	1.685	1.6
45	4	.192	.19
46	2	.062	.06
49	3	.051	.05
50	2	.233	.23
51	3	1.884	1.8
54	3	.261	.26
55	5	.342	.34
58	5	52.32	52.3
60	2	1.015	1.

TABLE XII.

*Total excretion of sugar.**(Intake 100 gms.)**Diabetic.*

No.	Hours	Sugar Gms.	Per cent. Exc.
63	3	.045	.04
64	3	.877	.41
66	4	.690	.69
68	4	3.218	3.2
69	5	4.678	4.7
70	5	7.51	7.6
71	6	1.279	1.2
73	4	1.25	1.2
79	4	3.04	3.
80	5	41.53	41.5
81	3	4.54	4.5
82	4	5.56	5.5
83	3	11.84	11.8
84	3	10.86	10.8
85	4	19.90	13.2
86	4	50.25	50.2
87	4	17.62	17.6
88	4	19.24	19.2
89	5	8.46	8.5
90	4	32.58	32.5
91	4	3.96	3.9
92	4	6.03	6.
93	4	4.55	4.5
94	3	5.06	5.
96	4	17.24	17.2
97	5	16.74	16.7
98	4	13.16	13.1
100	4	59.72	59.7

TABLE XIII.

A comparative study of blood sugar estimation done by the regular and the Epstein methods.

*Macro-Method**Epstein Method*

Plasma	Whole Blood	Corp. Sugar	Plasma	Whole Blood	Corp. Volume
112	112	—	—	124	—
183	183	—	—	308	—
180	184	—	—	310	—
137	151	—	—	240	—
88	120	—	—	212	—
64	84	—	—	100	—
132	130	—	—	240	—
254	250	—	—	340	—
256	250	—	—	344	—
241	230	—	—	280	—
280	207	—	—	220	—
150	146	—	—	134	—
155	154	—	—	121	—
214	214	—	—	190	—
267	261	—	—	243	—
334	319	—	—	328	—
334	319	—	—	324	—
	175	—	—	187	—
143	79	—	—	124	—
230	219	—	—	190	—
272	272	—	—	226	—
309	300	—	—	360	—
214	204	—	—	260	—
167	172	—	—	154	—
75	141	—	—	110	—
158	161	—	—	108	—
120	114	—	—	138	—
136	128	—	—	130	—
79	88	—	—	100	—
79	92	—	—	96	—
100	110	—	—	132	—
102	104	—	—	144	—
100	105	—	—	130	—
98	100	—	—	132	—
104	105	—	110	—	—
206	191	—	236	—	—
230	214	—	248	—	—
300	273	—	240	—	—
193	204	—	240	—	—
176	176	—	248	—	—
200	208	—	228	—	—
263	250	—	316	—	—

TABLE XIII. (*Continued*).*Macro-Method**Epstein Method*

Plasma	Whole Blood	Corp. Sugar	Plasma	Whole Blood	Corp. Sugar
333	333	—	208	—	—
250	234	—	348	—	—
192	200	—	240	—	—
193	200	—	272	—	—
73	75	—	78	—	—
163	167	—	184	—	—
150	150	—	154	—	—
69	70	—	65	—	—
68	71	—	67	—	—
60	71	—	65	—	—
81	111	—	85	60	—
135	136	—	105	120	—
111	120	—	87	90	—
75	81	—	77	67	—
72	79	—	70	69	—
71	71	—	80	55	—
75	91	—	65	74	—
161	161	—	140	110	—
171	172	—	150	104	—
94	111	—	73	60	—
35	37	—	65	50	—
75	85	—	50	74	—
89	108	116	75	67	—
163	182	164	176	106	—
140	150	156	134	85	—
128	129	131	101	70	—
95	105	134	66	102	—
98	104	104	66	105	—
400	411	352	420	444	—
567	519	460	580	580	—
598	578	468	592	584	—
645	598	500	680	680	—
579	506	428	620	600	—
506	486	414	560	580	—
424	455	364	460	460	—
129	135	122	109	125	—
202	196	167	231	—	—
233	225	—	273	285	—
291	315	258	336	378	—
308	291	263	364	429	—
296	312	261	253	354	—
98	102	104	73	—	—
163	161	153	94	103	—
133	132	120	106	101	—
131	131	126	105	115	—
53	78	75	64	64	—
72	86	85	98	76	—

TABLE XIV
RELATIVE BLOOD VOLUME AS CALCULATED FROM THE CORPUSCLE VOLUME

NON-DIABETIC

Number	Start			1/2 Hour			1 Hour			2 Hours			3 Hours			4 Hours			5 Hours			Rel. of Urine Output to Intake	
	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Urine In-crease, %	Urine De-crease, %
1	40	100	100	38	95	105	32	80	120	40	100	100	40	100	100	38	95	105	50.5	57.8	...
2	35	100	100	44	125	75	27	77	123	35	100	100	32	91	109	29	82	118	31.2
3	40	100	100	41	101	99	41	101	99	48	120	80	47	117	83	45	112	88
4	40	100	100	37	92	108	28	70	130	41	101	99	39	97	103	28	70	130	...	62	138	...	5.0
5	37	100	100	40	108	92	33	89	111	38	102	98	36	97	103	40	108	92	4.0	...
6	39	100	100	25	64	136	26	67	133	26	69	133	28	71	129	30	77	123	37.2	...
7	38	100	100	36	95	105	41	108	92	41	108	92	53	140	60	101.0
8	52	100	100	52	100	38	73	127	44	85	115	55	106	94	61.6	...
9	47	100	100	48	102	98	42	89	111	52	110	90	41	87	113	43	91	109	3.5	...
10	52	100	100	53	102	98	41	79	121	45	87	113	42	80	120	42	80	120	18.6
11	47	100	100	45	96	104	47	100	100	44	94	106	40	85	115
12	52	100	100	45	96	104	47	100	100	33	107	93	30	97	103	...	78	122	...	81.2
13	47	100	100	37	120	80	37	120	80	40	129	71	44	105	95	44	105	95	12.2
14	31	100	100	40	95	105	39	92	108	43	102	98	44	105	95	44	105	95	...	33	81.6
15	42	100	100	39	83	117	39	83	117	36	76	124	36	76	124	11.2
16	47	100	100	39	83	117	39	83	117	36	76	124	36	76	124	28.0
17	36	100	100	36	100	100	49	136	64	33	92	108	35	97	103
18	41	100	100	29	93	107	31	100	100	37	120	80	40	130	70	34	110	90	37.2
19	32	100	100	45	107	93	35	83	117	39	93	107	37	88	112	37	88	112
20	31	100	100	45	107	93	35	83	117	39	93	107	37	88	112	37	88	112	25.0
21	33	100	100	38	115	85	38	115	85	39	119	81	35	106	94	39	119	81	44
22	33	100	100	37	79	121	32	68	132	37	79	121	35	74	126	37	79	121
23	47	100	100	37	120	80	37	120	80	40	129	71	44	105	95	44	105	95
24	46	100	100	43	105	95	41	100	100	45	110	90	42	102	98	45	110	90	46.5	...	66.5
25	36	100	100	43	94	106	40	87	113	40	87	11	38	82	118	42	91	109	7.0
26	46	100	100	43	120	80	40	111	89	41	114	...	38	106	94	37	103	97
27	36	100	100	43	120	80	40	111	89	41	114	...	38	106	94	37	103	97
28	46	100	100	43	120	80	40	111	89	41	114	...	38	106	94	37	103	97
29	36	100	100	43	120	80	40	111	89	41	114	...	38	106	94	37	103	97
30	42	100	100	44	105	95	47	112	88	33	100	100	31	95	105	28.2
31	33	100	100	32	97	103	30	91	109	33	100	100	31	95	105	23.5
32	37	100	100	37	100	100	40	108	92	37	100	100	39	105	95	37	100	100
33	37	100	100	39	83	117	39	83	117	36	76	124	39	83	117
34	37	100	100	42	110	90	43	113	87	45	119	81	44	115	85	49	129	71
35	38	100	100	41	95	105	43	113	87	45	119	81	44	115	85	49	129	71
36	43	100	100	41	95	105	43	113	87	45	119	81	44	115	85	49	129	71
37	48	100	100	43	100	110	39	81	119	41	85	115	43	90	110	45	94	106
38	43	100	100	36	92	108	41	105	95	34	87	113	37	95	105	40	102	98
39	47	100	100	47	100	100	42	89	111	44	94	106	42	89	111	35	74	126
40	51	100	100	40	86	114	34	97	103	35	100	100	34	97	103	34	97	103
41	35	100	100	45	105	95	47	109	91	37	106	104	35	100	100	42	120	80
42	42	100	100	38	109	91	37	106	104	35	100	100	42	120	80
43	43	100	100	38	109	91	37	106	104	35	100	100	42	120	80
44	42	100	100	37	88	112	37	88	112	40	95	105	38	90	110	38	90	110
45	35	100	100	35	92	108	31	81	119	23	60	140
46	38	100	100	35	92	108	31	81	119	23	60	140
47	35	100	100	36	100	100	38	105	95	36	100	100	38	10	95	40	111	89
48	42	100	100	47	124	76	51	134	66	57	150	50	68	179	21	48	126	74
49	38	100	100	47	124	76	51	134	66	57	150	50	68	179	21	48	126	74
50	38	100	100	47	124	76	51	134	66	57	150	50	68	179	21	48	126	74
51	36	100	100	47	124	76	51	134	66	57	150	50	68	179	21	48	126	74
52	38	100	100	47	124	76	51	134	66	57	150	50	68	179	21	48	126	74

Number	Start			¼ Hour			1 Hour			2 Hours			3 Hours			4 Hours			5 Hours			Rel. of Urine Output to Intake	
	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Corp. Vol., %	Rel. Corp., %	Rel. Blood Vol., %	Urine In-crease, %	Urine De-crease, %
56	39	100	100	47	120	80	34	92	108	80	47	120	50	128	72	45	115	85	20.8
59	37	100	100	35	95	105	35	95	105	105	35	95	36	97	103	33	89	111	36.8
61	48	100	100	59	123	77	43	90	110	121	79	121	43	90	110	40.0
67	35	100	100	41	117	83	32	91	109	114	30	86	32	91	109	31	89	111	39.0	...
69	49	100	100	44	90	110	37	75	125	...	41	119	37	75	125	47	96	104	...	81	119	...	9.0
70	38	100	100	35	92	108	37	75	125	116	32	84	37	97	103	34	90	110	8.5
72	38	100	100	40	105	95	39	102	98	103	37	97	37	97	103	40	105	95	37.7
73	33	100	100	40	121	79	40	121	79	7.0
74	35	100	100	33	95	105	32	91	109	100	35	100	36	103	97	64.5
75	43	100	100	41	95	105	39	90	110	107	40	93	34	79	121	34	79	121	59.4
76	46	100	100	44	95	105	47	102	98	102	33	98	33	72	128	23.0
77	40	100	100	35	87	113	39	97	103	107	37	93	38	95	105	36	90	110	...	38	95	105	28.0
78	47	100	100	48	102	98	50	106	94	109	43	91	41	87	113	37.0
79	38	100	100	40	105	95	40	105	95	105	36	95	43	113	98	42	110	90	60.0
80	48	100	100	50	104	96	45	94	106	49	49	102	98	90	110	47	98	102	43	90	110	...	15.5
81	42	100	100	42	100	100	38	90	110	109	39	93	40	95	105	39	93	107	40.0
82	48	100	100	44	91	109	44	91	109	47	98	102	43	90	110	40	83	117	15.8
83	40	100	100	40	100	100	39	98	102	102	36	90	41	102	98	32.5
84	46	100	100	46	100	100	46	100	100	100	40	87	48	104	96	45	98	102	19.0	...
85	48	100	100	50	104	96	42	87	113	115	41	85	44	83	117	44	92	108	6.4	35.0
86	40	100	100	42	105	95	41	100	100	100	41	102	36	69	131	44	85	115	0.0	0.0
87	52	100	100	41	79	121	121	31	60	36	70	130	40	85	115	...	38	95	105	8.8
88	47	100	100	43	91	109	44	94	106	106	43	91	37	92	108	44	95	105
89	40	100	100	35	87	113	39	97	103	103	41	102	98	95	105	35	100	100	1.1	23.0
90	46	100	100	46	100	100	43	94	106	106	42	91	33	95	105	35	98	102	63.5
91	35	100	100	33	94	106	106	25	71	36	95	105	42	98	102	40.0
92	43	100	100	43	100	100	38	88	112	124	41	86	41	95	105	38	100	100	44.4
93	38	100	100	37	97	103	35	92	108	108	37	97	36	95	105	38	100	100	19.7
94	45	100	100	47	105	95	43	95	105	105	40	89	41	91	109	41	91	109	27.4
95	36	100	100	36	100	100	47	130	70	52	52	144	43	120	80	57	158	42	7.4
96	47	100	100	45	96	104	44	94	106	106	43	91	40	85	115	42	89	111
97	37	100	100	38	103	97	39	106	94	111	41	111	38	103	97	41	111	89	...	38	86	114	...
98	44	100	100	41	93	107	35	80	120	116	37	84	28	64	136	37	84	116	...	49	98	102	40.0
99	50	100	100	55	110	90	51	102	98	108	46	92	52	104	96	52	104	96	9.5
100	47	100	100	44	93	107	39	83	117	119	38	81	40	85	115	47	100	100

TABLE XVI.

*Plasma (relative total blood) volume during
glucose tolerance test.*

Non-Diabetic.

Increase of Plasma

At	10	20	30	40	50	Per Cent
$\frac{1}{2}$ hr.	13	5	1	1	—	No. of cases
1 hr.	4	10	4	2	—	
2 hrs.	6	5	3	2	—	
3 hrs.	10	6	5	—	—	
4 hrs.	11	5	5	1	—	
5 hrs.	—	—	1	1	—	

Decrease of Plasma

At	10	20	30	40	50	Per Cent
$\frac{1}{2}$ hr.	10	3	2	—	—	No. of cases
1 hr.	7	5	—	2	—	
2 hrs.	8	5	1	—	1	
3 hrs.	8	2	1	—	—	
4 hrs.	9	3	2	1	—	
5 hrs.	1	1	—	—	—	

Diabetic.

Increase of Plasma

At	10	20	30	40	50	Per Cent
$\frac{1}{2}$ hr.	12	2	—	—	—	No. of cases
1 hr.	17	4	2	—	—	
2 hrs.	15	9	2	1	—	
3 hrs.	14	3	4	2	—	
4 hrs.	11	7	1	—	—	
5 hrs.	4	2	—	—	—	

Decrease of Plasma

At	10	20	30	40	50	Per Cent
$\frac{1}{2}$ hr.	9	2	2	—	—	No. of cases
1 hr.	6	—	1	—	—	
2 hrs.	3	2	—	—	1	
3 hrs.	6	3	1	—	—	
4 hrs.	3	3	1	—	—	
5 hrs.	—	—	—	—	—	

TABLE XVII

A STUDY OF THE RELATION OF CORPUSCLE VOLUME TO BLOOD SUGAR CONCENTRATION

DIABETIC

HENRY J. JOHN

527

No.	B. Sug. 0 hr.	C V %	% Inc.	% Dec.	B. Sug. 1 hr.	C V %	% Inc.	% Dec.	B. Sug. 2 hrs.	C V %	% Inc.	% Dec.	B. Sug. 3 hrs.	C V %	% Inc.	% Dec.	B. Sug. 4 hrs.	C V %	% Inc.	% Dec.	B. Sug. 5 hrs.	C V %	% Inc.	% Dec.
56	128	39	186	47	20	..	15	50	28	..	127	50	28	..	145	45	15
59	164	37	192	35	205	47	20	..	147	36	100	33
61	115	48	145	59	23	..	230	35	184	38	86	43
67	109	35	252	41	17	..	330	38	226	30	122	31
69	126	49	208	44	348	30	18	32	25	37
70	194	38	219	35	367	40	285	37	170	47
72	132	38	254	40	5	..	309	32	208	37	164	34
73	117	33	192	40	21	..	241	37	334	36	186	40
74	155	35	214	33	334	35	334	36	2
75	104	43	230	41	300	40	193	34	176	34
76	134	46	230	44	309	45	214	33
77	200	40	263	35	250	37	192	38	194	36
78	250	47	334	47	438	43	214	41
79	193	38	346	40	5	..	280	36	238	43	13	..	184	42
80	306	48	340	50	4	..	344	49	2	..	265	43	224	47
81	155	42	374	38	368	39	306	40	210	39
82	196	48	356	44	411	47	310	43	237	40
83	203	40	300	40	377	36	405	41	2
84	233	46	323	46	420	40	265	48	4	..	157	45
85	237	48	383	50	4	..	485	41	428	44	273	44
86	344	40	449	42	5	..	464	41	2	..	403	44	10	..	335	46	15
87	286	52	425	31	381	36	309	44
88	202	47	368	43	21	43	557	37	279	40
89	230	40	373	35	511	41	3	..	428	42	342	44
90	264	45	460	45	522	42	379	33	324	35
91	210	35	318	25	308	41	296	42
92	129	43	202	43	291	37	318	36	280	38
93	198	38	262	37	330	37	359	41	279	41
94	198	45	298	47	4	..	351	40	342	43	20	..	308	57	58
95	178	36	250	36	398	52	44	..	350	42	302	42
96	271	47	414	45	425	43	358	38	405	41
97	282	37	416	38	2	..	423	41	10	..	428	38	370	37
98	313	44	366	41	467	37	357	28	370	37
99	400	50	567	55	10	..	645	46	519	52	4	..	506	52
100	350	47	491	44	636	38	607	40	530	47

TABLE XIX.

*Classification of Individuals as Determined by
Glucose Tolerance Test.*

Non-diabetic		(4) Diabetic
(Blood sugar becomes normal within 3 hours after ingestion of 100 gm. of glucose.)		(Blood sugar becomes normal more than 3 hours (usually 6-9 hours) after the ingestion of 100 gm. of glucose. The rise and fall of the blood sugar curve are slow.)
(1) Strong Normal	(2) Normal	(3) Weak Normal (Pre-diabetic)
After ingestion of 100 gms. glucose the blood sugar curve appears as practically a straight line on or below the normal level.	Maximum rise of the blood sugar curve appears $\frac{1}{2}$ hour after ingestion of 100 gms. of glucose with a prompt fall to the normal within from 1 to 1- $\frac{1}{2}$ hours.	Maximum rise of blood sugar curve from $\frac{1}{2}$ -1- $\frac{1}{2}$ hours after ingestion of 100 gms. glucose, the curve returning to the normal level in about three hours.

TABLE XX
A SURVEY OF THE 100 CASES SUBMITTED TO THE GLUCOSE TOLERANCE TEST

Number	Sex	Age	Occupation	History of Diabetes in Family	Measles	Rheumatism	Scarlet Fever	Typhoid	Tuberculosis	Tonsillitis	Influenza	Diphtheria	Pneumonia	Pleurisy	Malaria	Appendectomy	Fasting Blood Sugar	Glycosuria	Wassermann	Gain in Weight	Loss in Weight	Phenalsulphobiphtalein Renal Test	Blood Pressure	Blood Urea	Blood Uric Acid	Plasma Chlorides	Blood Creatinin	Chief Complaint	Diagnosis of the Case
1	M	16	Schoolboy	negative	0	0	0	0	0	0	0	0	0	0	0	0	63	0	0	0	0	0	12	1.76	585	0.5	none	Normal	
2	M	24	Clerk	negative	0	0	0	0	0	0	0	0	0	0	0	0	82	0	0	0	0	0	15	15	543	0	Freq urin.	Diab. insip. recovered	
3	M	51	Merchant	negative	0	0	0	0	0	0	0	0	0	0	0	0	75	0	0	0	0	0	14	14	583	0	Loss vitality	Hypopituitarism	
4	F	46	Housewife	Mother, Aunt	0	0	0	0	0	0	0	0	0	0	0	0	78	0	0	0	0	0	14	14	605	0	Tired, sleepy	Normal	
5	M	22	Baker	negative	0	0	0	0	0	0	0	0	0	0	0	0	74	0	0	0	0	0	14	14	573	0	Weakness	Hypopituitarism	
6	M	44	Physician	Father	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	32	3.6	575	2.0	Diabetes	Normal	
7	M	42	Sailor	negative	0	0	0	0	0	0	0	0	0	0	0	0	126	0	0	0	0	0	126/80	32	3.6	565	2.0	Mass in abd.	Splenom. leucemia
8	M	29	Physician	Paternal ancestors	0	0	0	0	0	0	0	0	0	0	0	0	86	0	0	0	0	0	110/70	25	2.0	574	1.1	Diabetes	Neurosis
9	M	16	Schoolboy	negative	0	0	0	0	0	0	0	0	0	0	0	0	81	0	0	0	0	0	122/72	5	2.8	585	0.8	Pain abd.	Normal
10	F	22	Telephone op.	negative	0	0	0	0	0	0	0	0	0	0	0	0	102	0	0	0	0	0	130/80	14	2.3	555	1.1	None	Normal
11	M	26	Physician	Uncle	0	0	0	0	0	0	0	0	0	0	0	0	107	0	0	0	0	0	18	18	2.4	565	1.1	Numness	No disease
12	F	26	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	121	0	0	0	0	0	15.7	15.7	515	0	Glycosuria	Renal permeability	
13	M	22	Clerk	negative	0	0	0	0	0	0	0	0	0	0	0	0	111	0	0	0	0	0	130/70	18	4.20	501	0	Headaches	Renal permeability
14	M	34	Salesman	Father, Brother, Uncle	0	0	0	0	0	0	0	0	0	0	0	0	89	0	0	0	0	0	55/15	100/58	2	322	0	Glycosuria	Renal permeability
15	F	40	Housewife	Brother	0	0	0	0	0	0	0	0	0	0	0	0	90	0	0	0	0	0	100/58	2	322	0	Glycosuria	Renal permeability	
16	F	18	Schoolgirl	negative	0	0	0	0	0	0	0	0	0	0	0	0	84	0	0	0	0	0	100/58	2	322	0	Glycosuria	Renal permeability	
17	M	23	Student	negative	0	0	0	0	0	0	0	0	0	0	0	0	99	0	0	0	0	0	15.7	15.7	515	0	Glycosuria	Renal permeability	
18	F	17	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	120	0	0	0	0	0	15.7	15.7	515	0	Glycosuria	Renal permeability	
19	F	19	Student	Mother	0	0	0	0	0	0	0	0	0	0	0	0	94	0	0	0	0	0	15.7	15.7	515	0	Glycosuria	Renal permeability	
20	F	19	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	95	0	0	0	0	0	102/60	19	398	0	Boils	Obesity	
21	M	34	Plumber	negative	0	0	0	0	0	0	0	0	0	0	0	0	95	0	0	0	0	0	102/60	19	398	0	Boils	Obesity	
22	M	36	Physician	negative	0	0	0	0	0	0	0	0	0	0	0	0	128	0	0	0	0	0	120/70	18	355	1.8	Diabetes	Varicose veins	
23	M	36	Steel worker	negative	0	0	0	0	0	0	0	0	0	0	0	0	103	0	0	0	0	0	33	3.5	655	1.8	Diabetes	Normal	
24	F	38	Stenographer	Mother	0	0	0	0	0	0	0	0	0	0	0	0	136	0	0	0	0	0	17	17	467	0	Lassitude	Normal	
25	F	35	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	150/90	10	1.4	585	0.9	Thirst	Syphilis
26	F	24	Housewife	Uncle mat.	0	0	0	0	0	0	0	0	0	0	0	0	98	0	0	0	0	0	18	3.6	595	0.7	Diabetes	Normal	
27	F	31	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	10	1.3	635	0.9	Skin disease	Sebor. dermatitis	
28	M	54	Farmer	negative	0	0	0	0	0	0	0	0	0	0	0	0	98	0	0	0	0	20/15	140/90	4	555	0	Glycosuria	Normal	
29	M	41	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	73	0	0	0	0	0	15	2.6	555	0.7	Kidney troub.	Acromegaly	
30	M	24	Clerk	negative	0	0	0	0	0	0	0	0	0	0	0	0	94	0	0	0	0	0	26	2.8	545	1.1	None	Normal	
31	F	35	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	95	0	0	0	0	0	19	1.0	595	1.6	None	Normal	
32	F	32	Clerk	negative	0	0	0	0	0	0	0	0	0	0	0	0	103	0	0	0	0	0	29	2.9	502	0	Obesity	Renal permeability	
33	F	33	Teacher	Fath. Grdm. pat.	0	0	0	0	0	0	0	0	0	0	0	0	97	0	0	0	0	0	29	2.9	613	1.4	Diabetes	Normal	
34	F	30	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	98	0	0	0	0	0	160/10	023	1.6	558	1.2	Swollen leg	Myocarditis
35	F	35	Nurse	negative	0	0	0	0	0	0	0	0	0	0	0	0	89	0	0	0	0	0	23/15	150/90	23	855	0	Cough	Chr. nephritis
36	M	50	Business man	negative	0	0	0	0	0	0	0	0	0	0	0	0	112	0	0	0	0	0	120/80	21	615	0	Ref. Life Ins	Renal permeability	
37	M	50	Policeman	negative	0	0	0	0	0	0	0	0	0	0	0	0	94	0	0	0	0	0	30	3.0	595	1.2	Diff. walking	Periosteal sarcoma	
38	F	39	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	139	0	0	0	0	58	30	574	0	Headaches	Renal permeability		
39	F	66	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	124	0	0	0	0	0	30	3.0	574	0	Rheumatism	Renal permeability	
40	M	36	Salesman	negative	0	0	0	0	0	0	0	0	0	0	0	0	111	0	0	0	0	0	130/90	27	4.4	625	1.2	Prur. vulv.	Normal
41	F	48	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	110	0	0	0	0	0	128/88	39	3.0	595	1.2	Freq. urin.	Prostat. Obstruct.
42	M	52	Labourer	negative	0	0	0	0	0	0	0	0	0	0	0	0	103	0	0	0	0	0	108/64	8	1.8	586	0	Pain abdom.	Neurosis
43	F	43	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	76	0	0	0	0	0	180/95	17	685	0	Nervousness	Renal permeability	
44	F	46	Housewife	negative	0	0	0	0	0	0	0	0	0	0	0	0	98	0	0	0	0	0	40/	200/100	028	570	0	Goitre	Myxedema
45	M	64	Insurance	negative	0	0	0	0	0	0	0	0	0	0	0	0	82	0	0	0	0	0	180/95	17	685	0	Palpitation	Hypertension	

[illegible]

• Stands for positive

CHART I.
Percentage of urinary output to water intake
Nondiabetic.

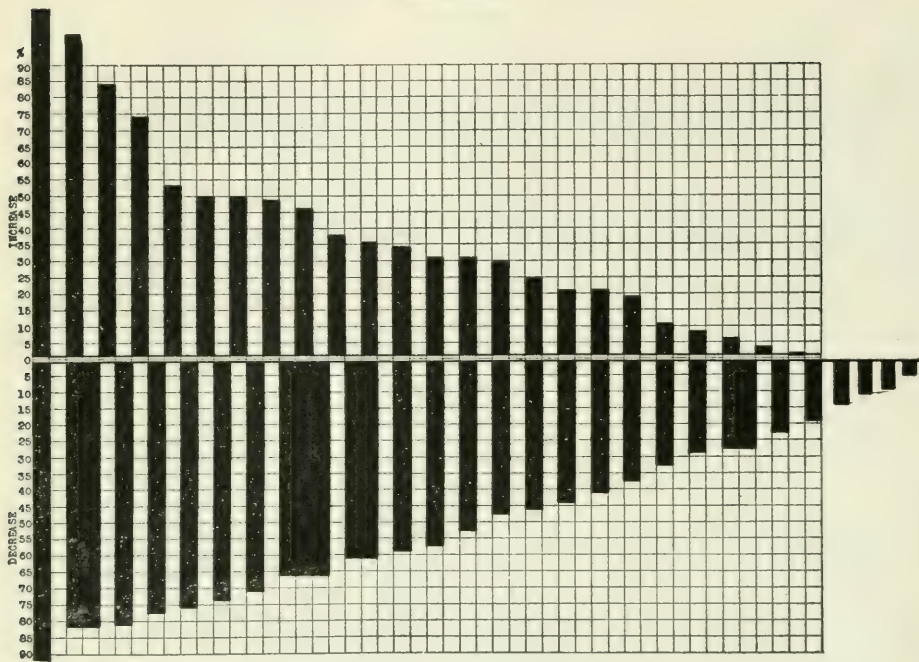


CHART II.
Percentage of urinary output to water intake
Diabetic.

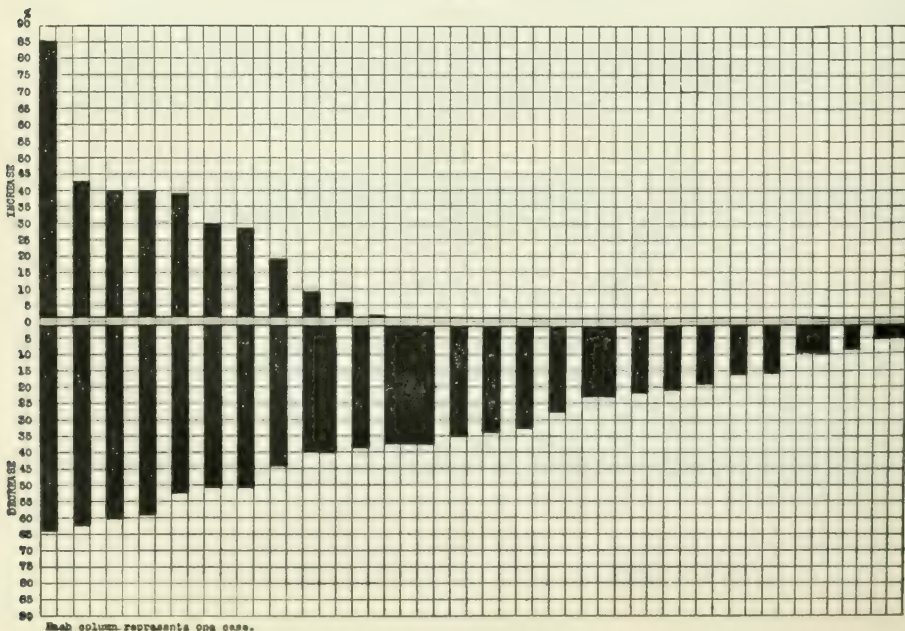


CHART III.

Comparison in Diabetics and in Non-Diabetics of periods within which highest blood sugar rise was reached after the ingestion of glucose.

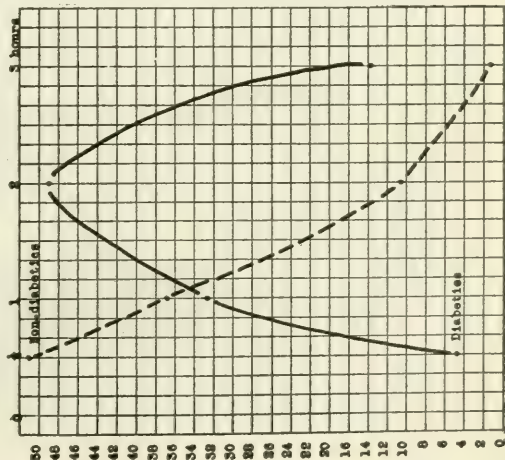
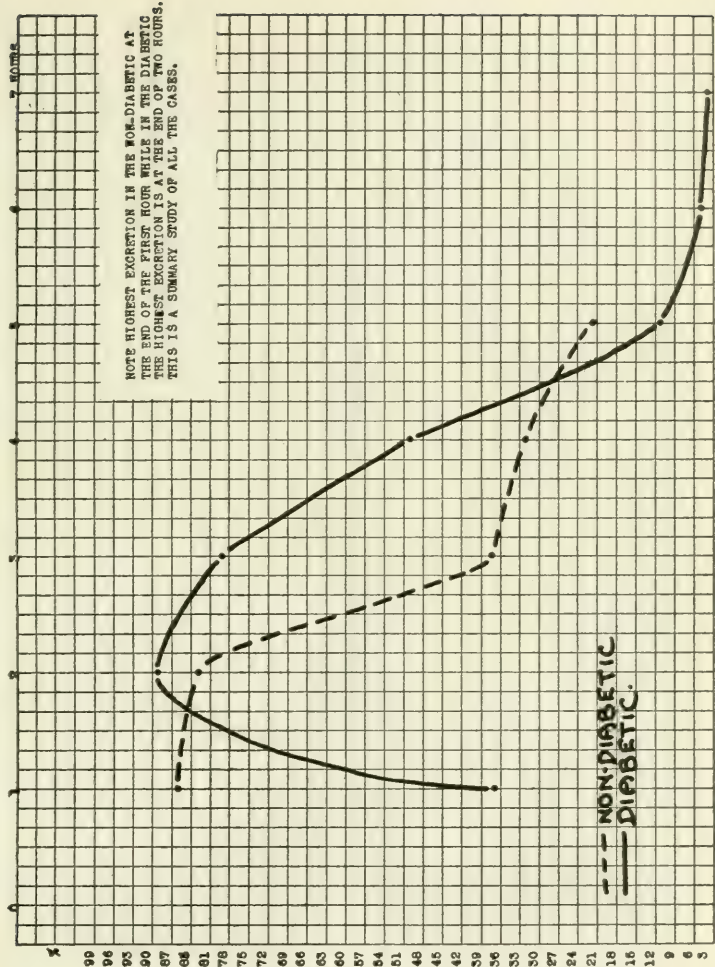


CHART IV.

The relation between the sugar excretion in the Diabetic and in the Non-Diabetic.



NOTE HIGHEST EXCRETION IN THE NON-DIABETIC AP-
PEARS AT THE END OF THE FIRST HOUR.
THE HIGHEST EXCRETION IN THE DIABETIC
APPEARS AT THE END OF TWO HOURS.
THIS IS A SUMMARY STUDY OF ALL THE CASES.

CHART V.
Relative number of cases without and with glycosuria at different blood sugar levels.

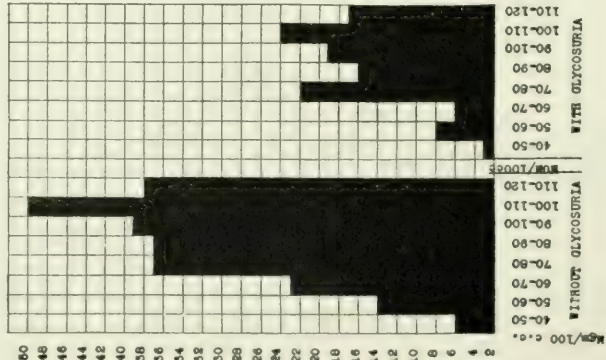


CHART VI.

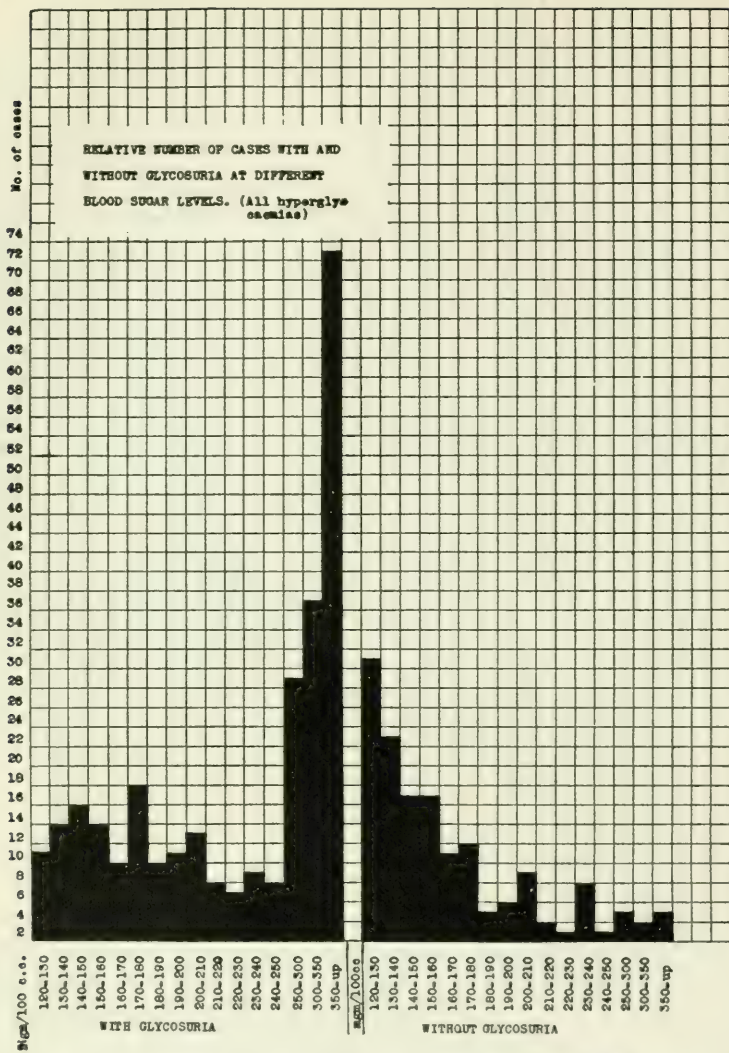


CHART VII
TOTAL SUGAR INTAKE AND OUTPUT DURING THE PERIOD OF GLUCOSE TOLERANCE TEST
MONDAY BEZIC.

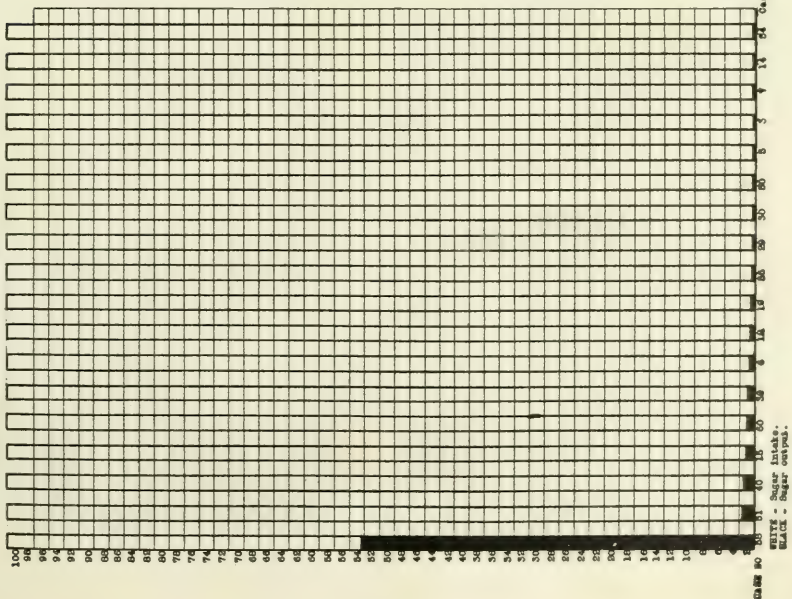
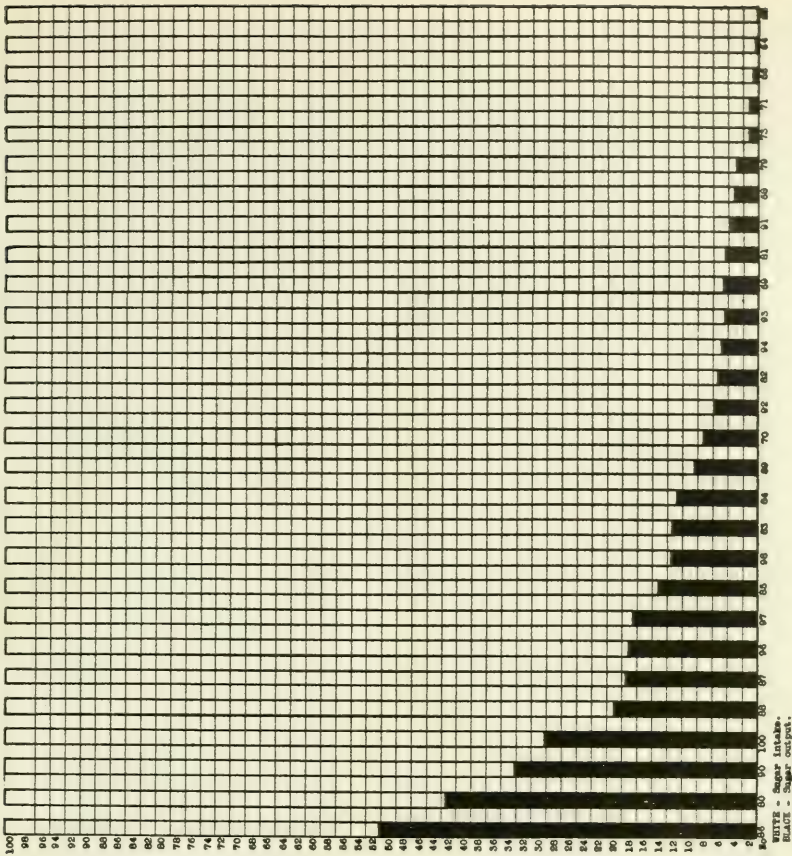
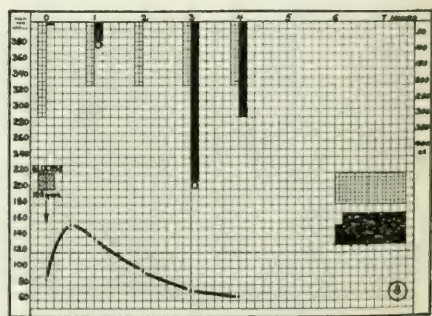
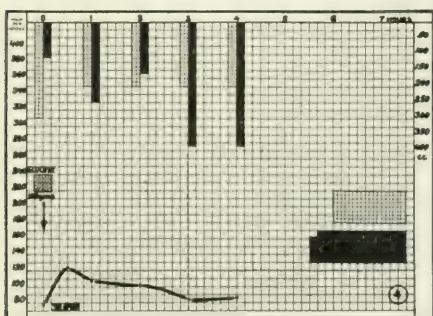
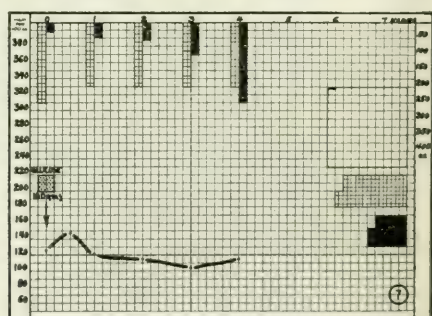
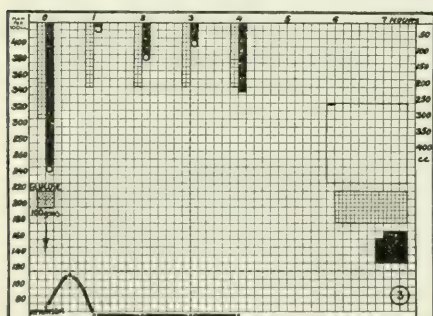
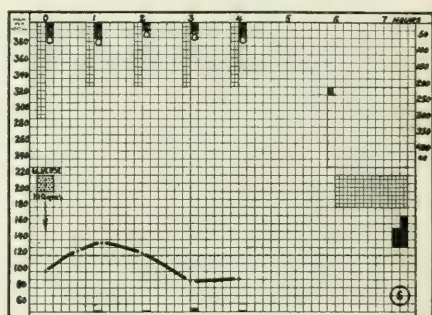
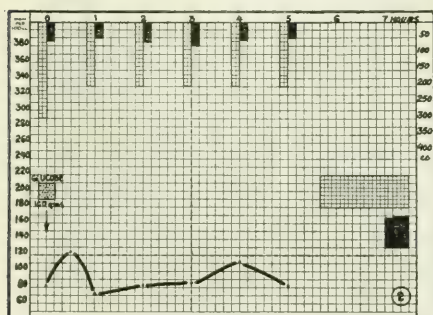
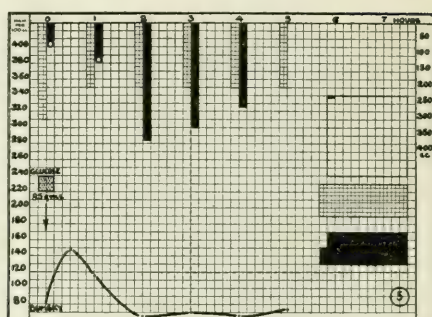
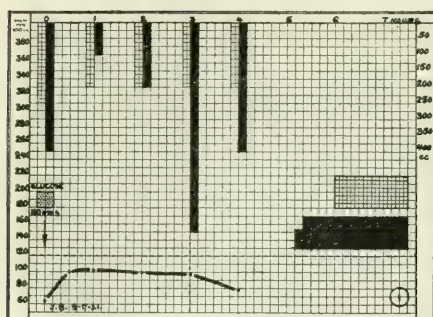
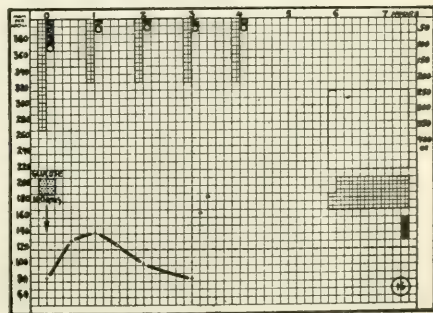
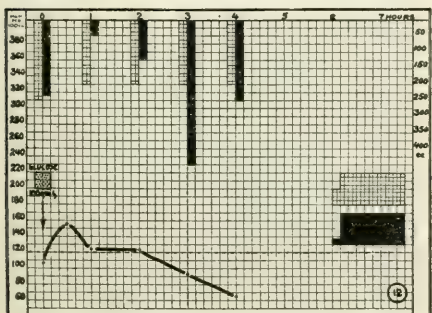
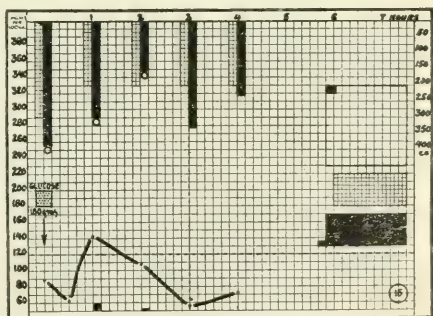
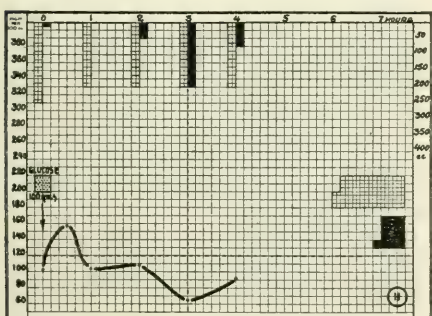
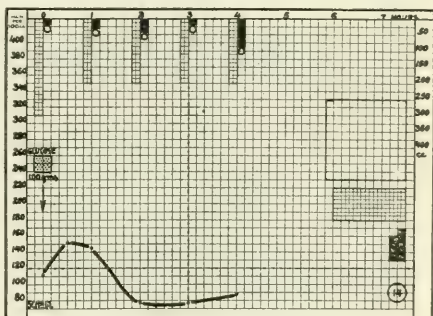
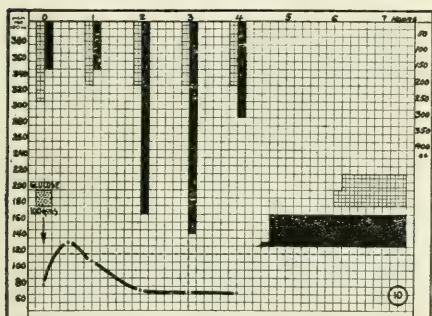
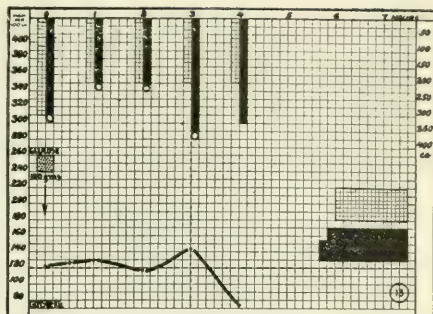
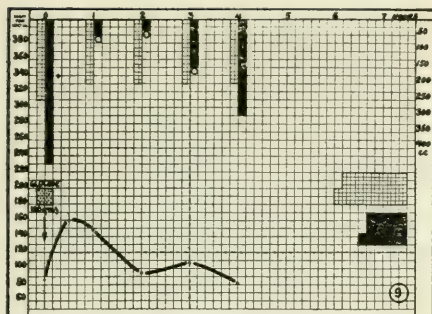
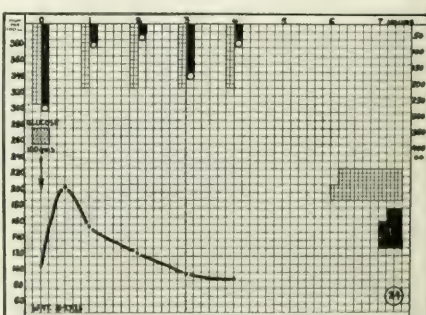
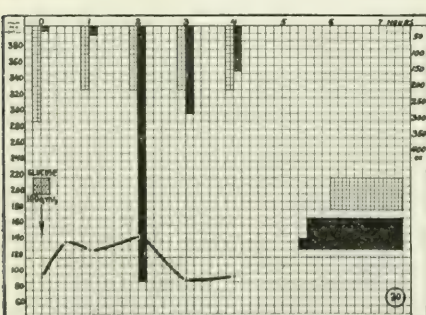
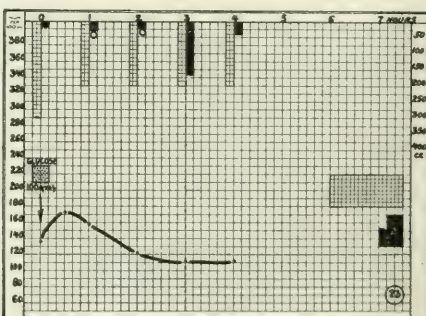
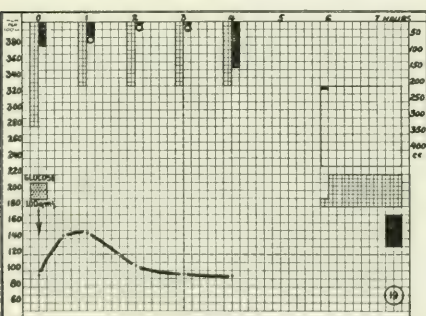
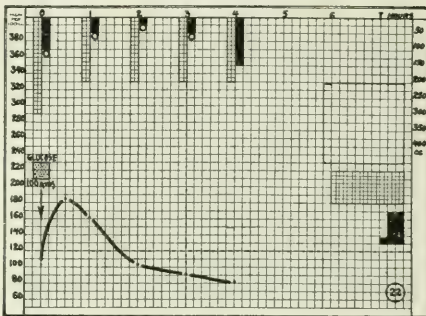
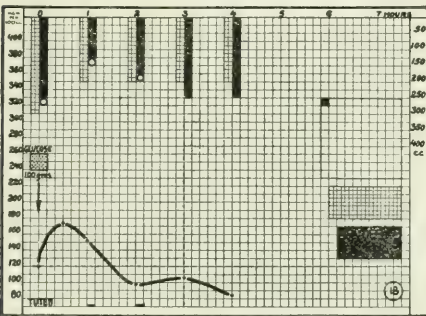
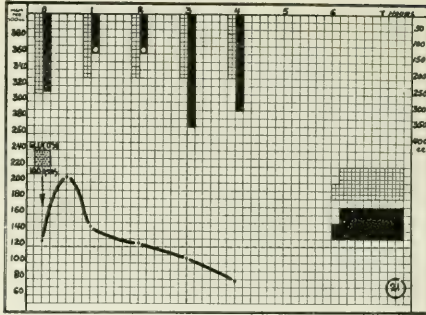
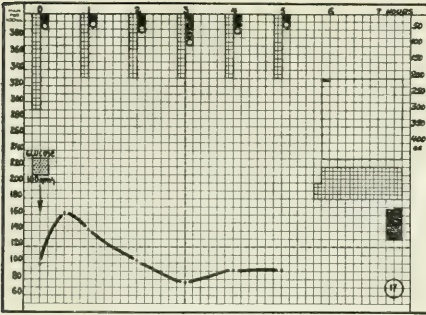


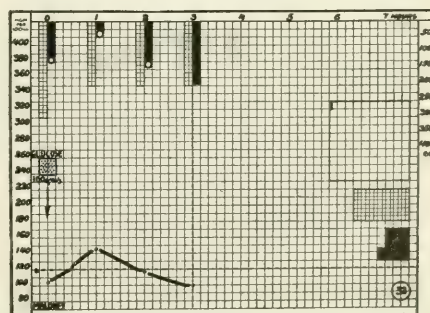
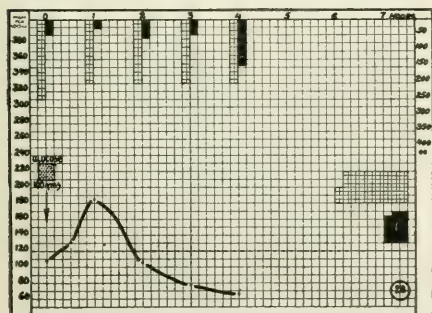
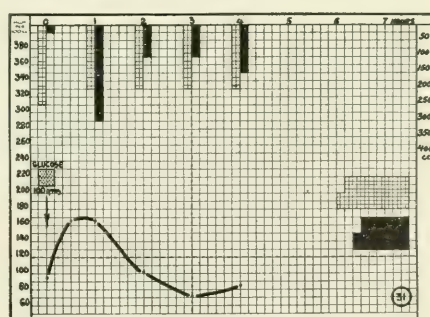
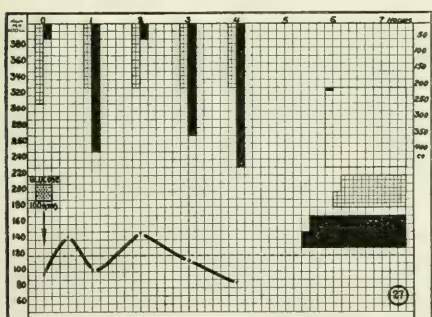
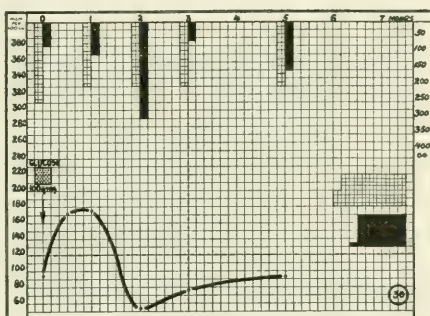
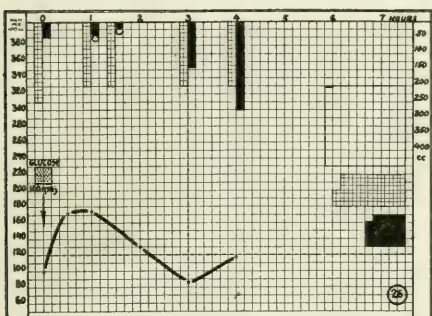
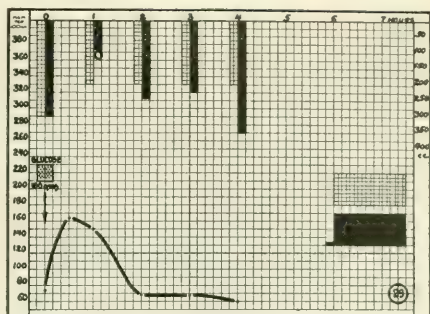
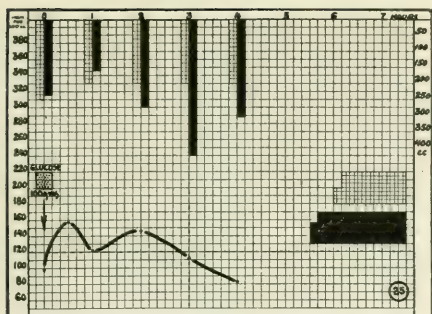
CHART VIII
TOTAL SUGAR INTAKE AND OUTPUT DURING THE PERIOD OF GLUCOSE TOLERANCE TEST
TUESDAY.

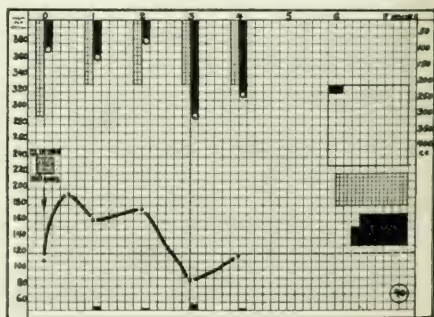
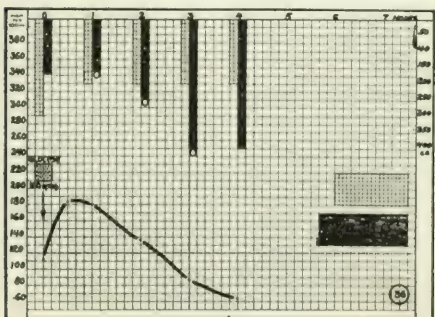
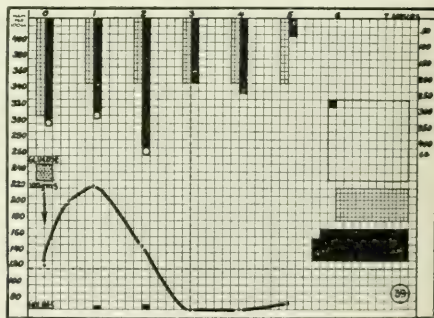
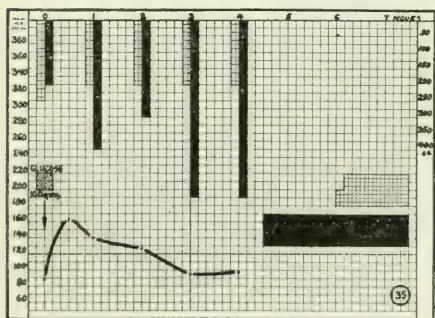
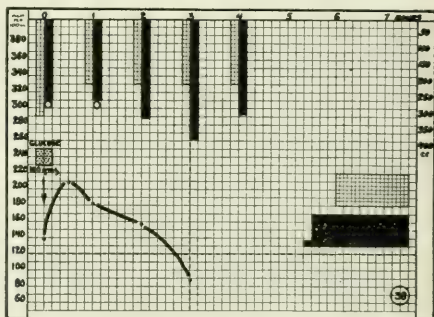
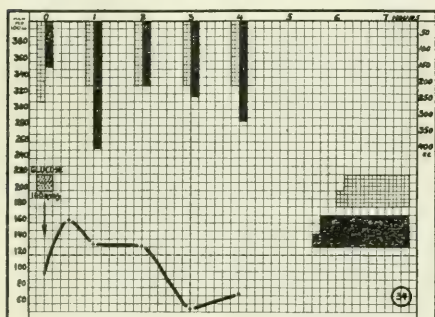
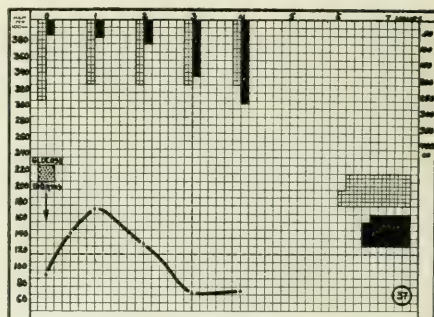
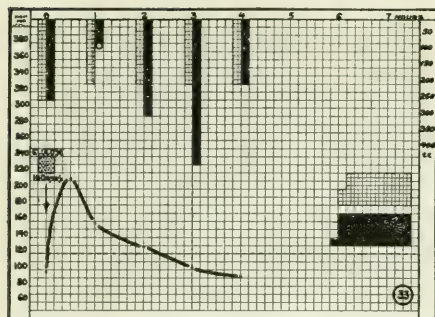


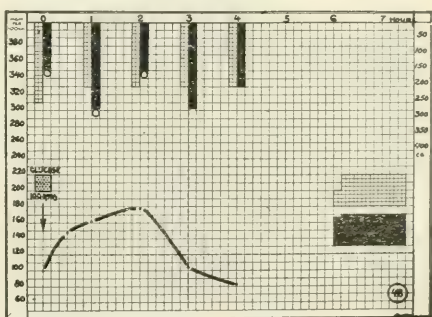
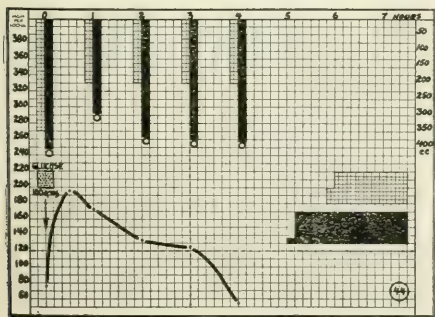
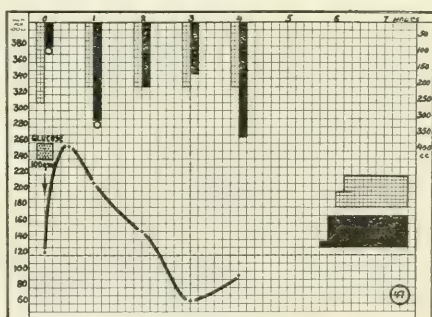
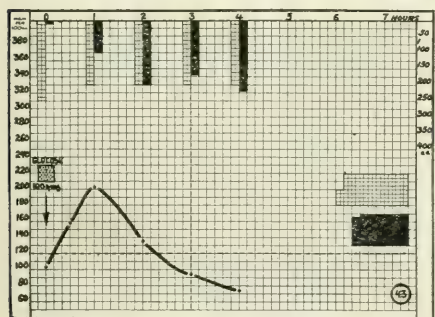
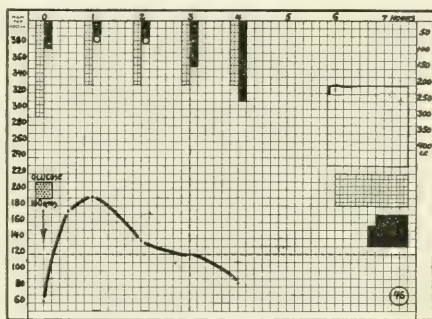
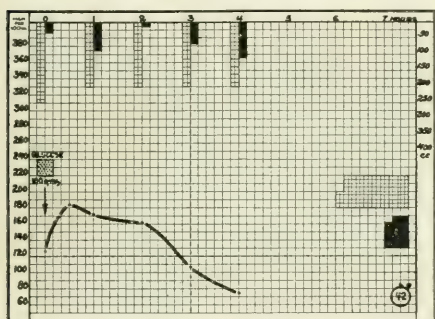
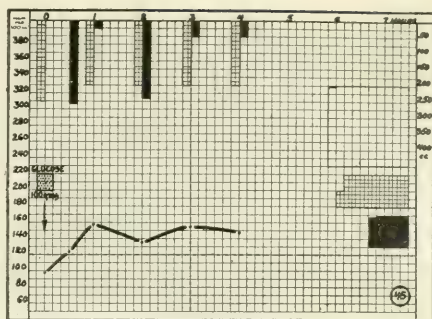
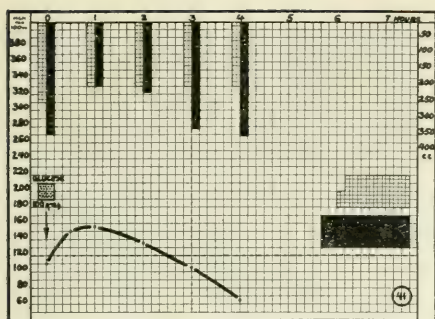


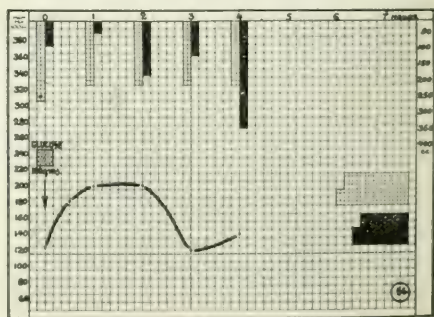
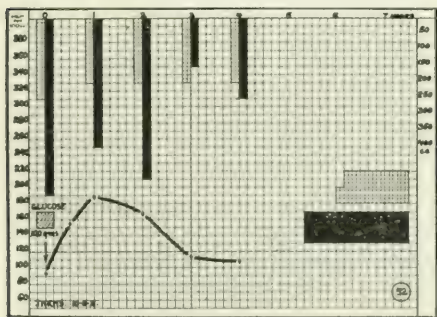
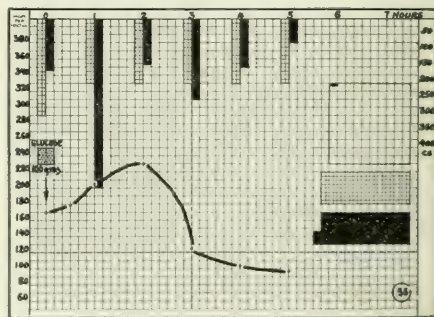
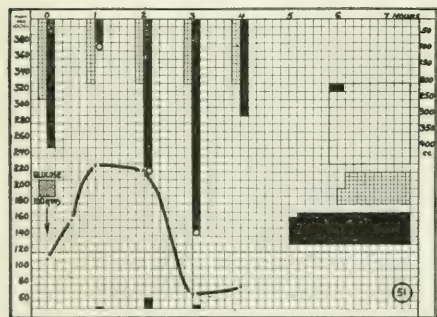
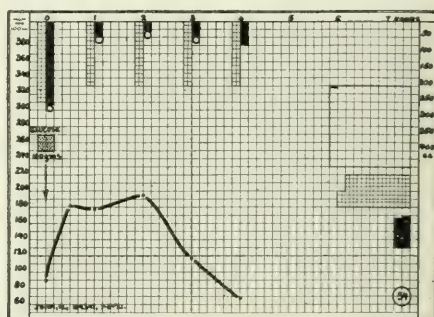
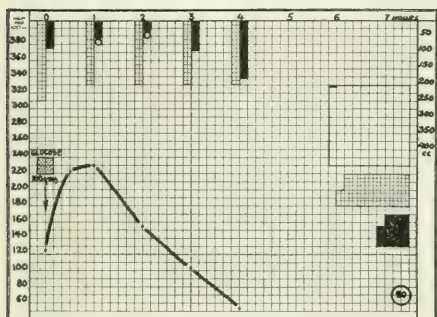
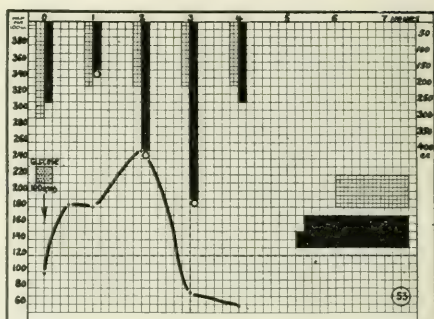
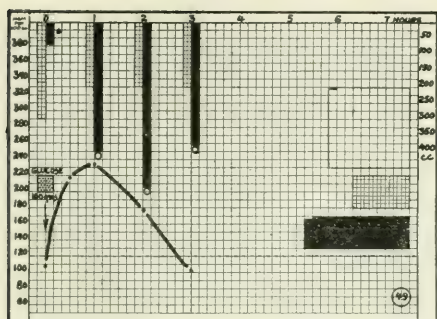


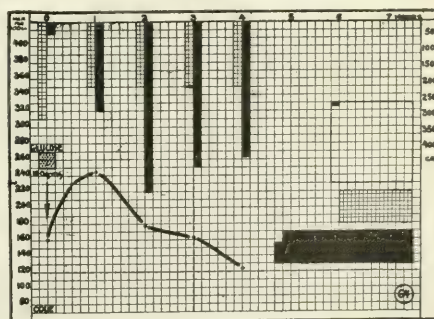
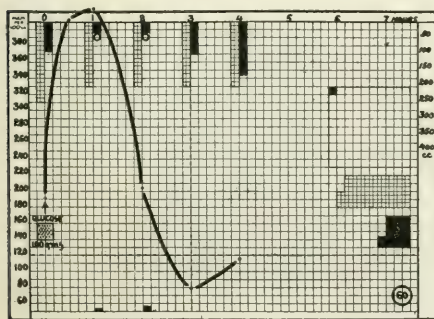
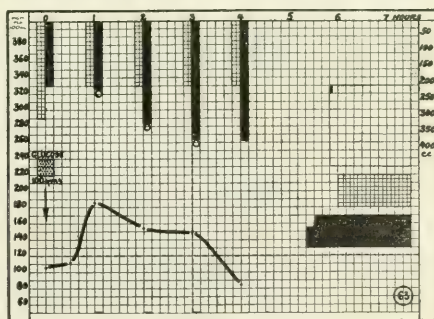
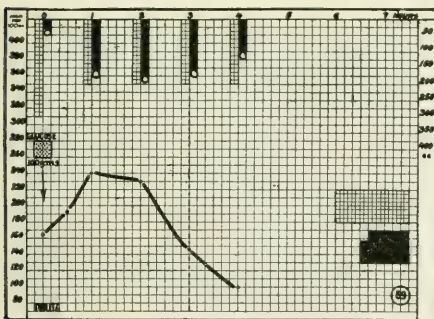
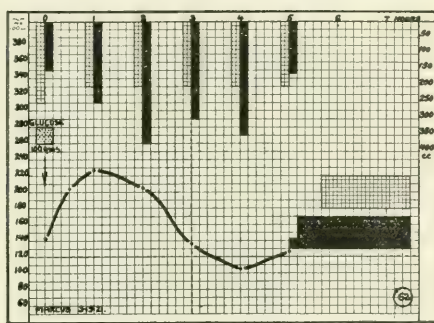
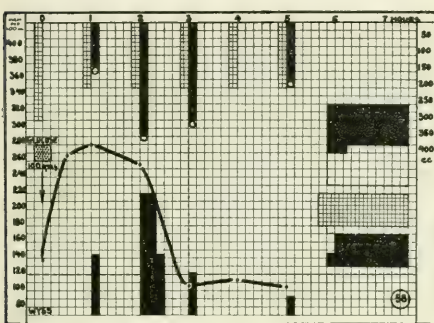
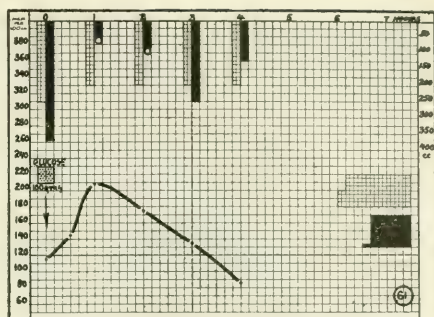
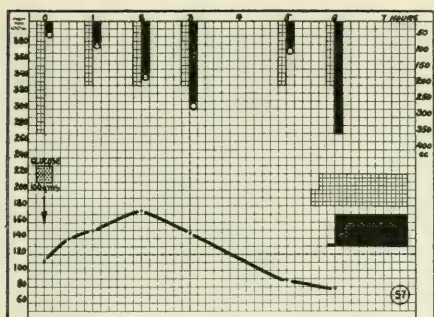


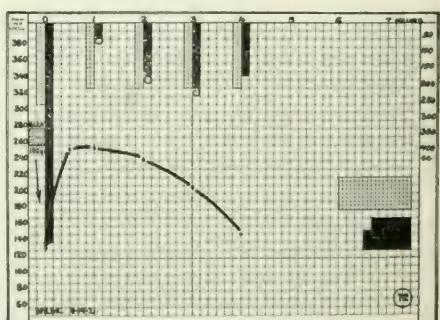
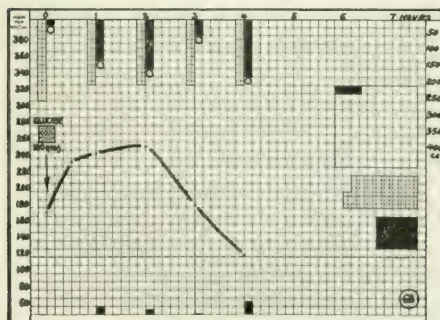
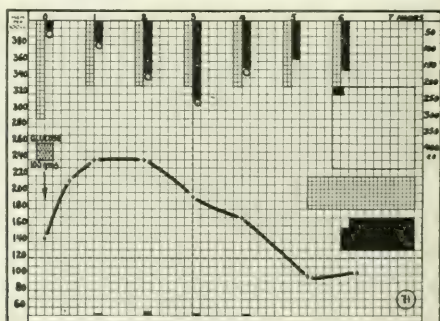
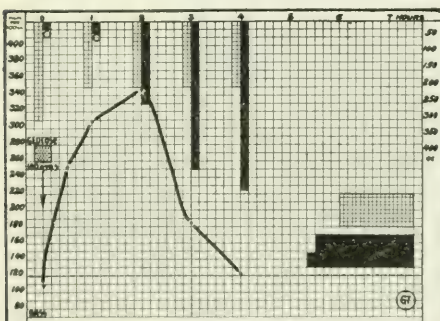
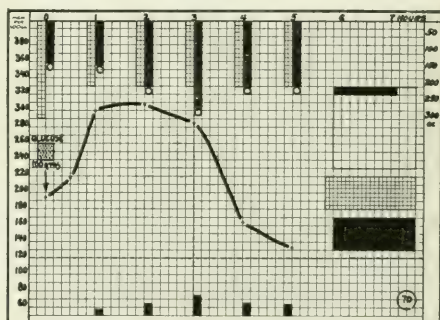
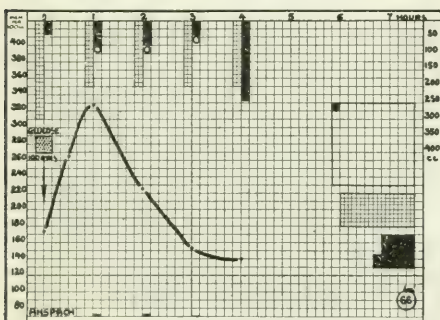
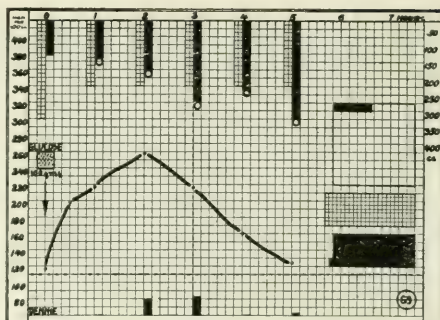
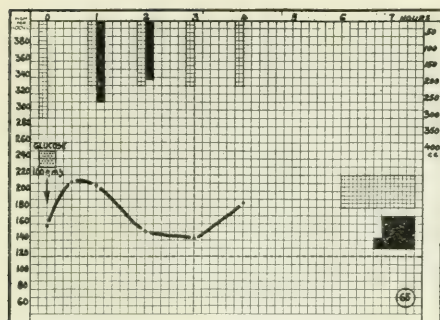


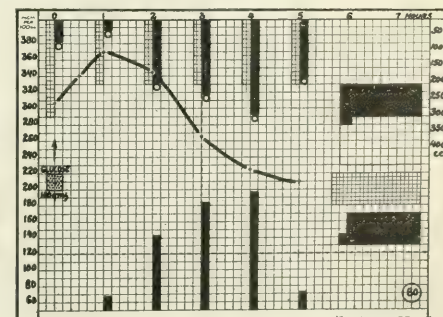
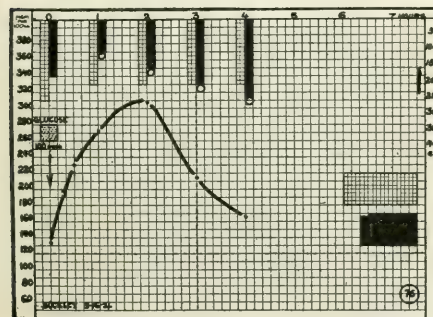
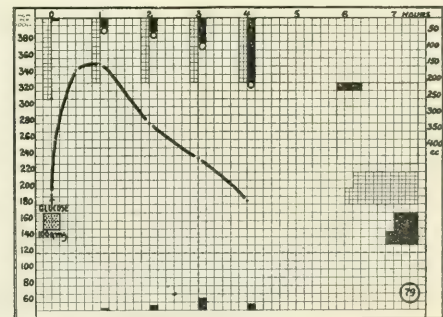
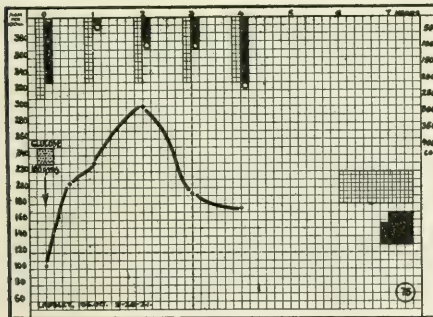
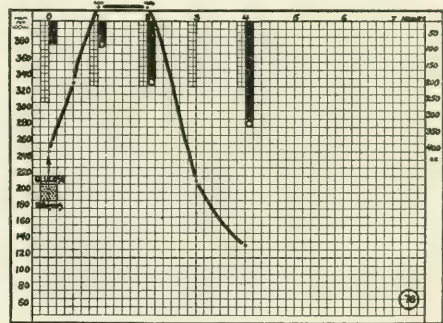
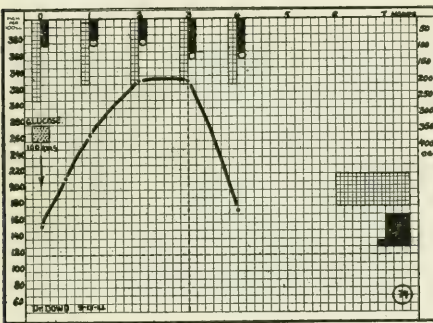
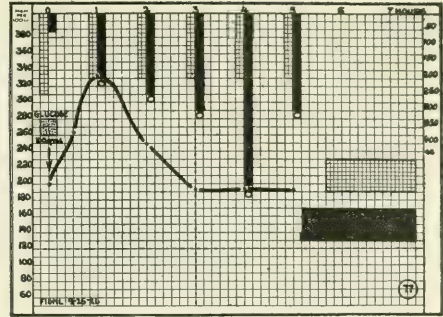
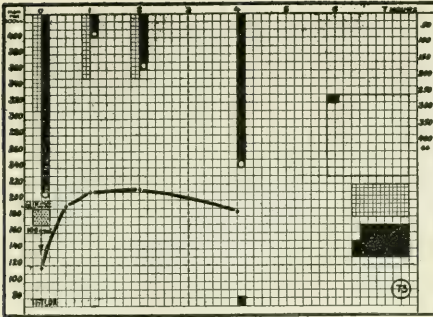


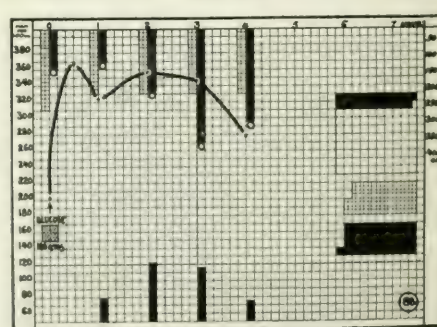
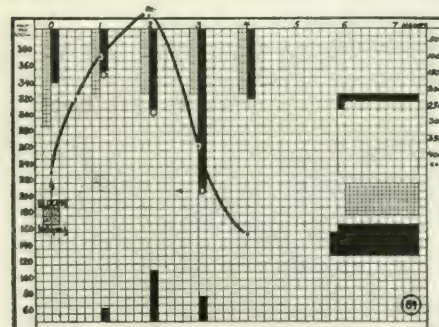
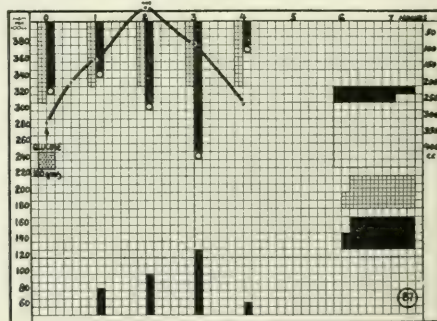
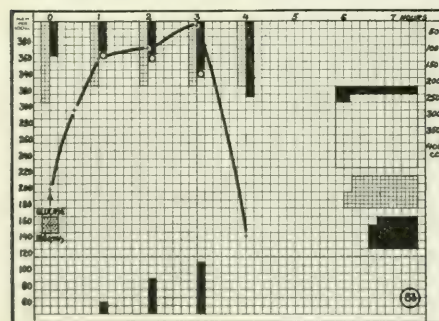
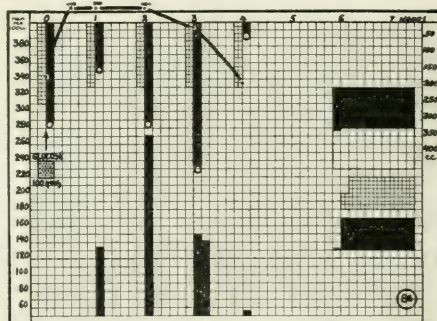
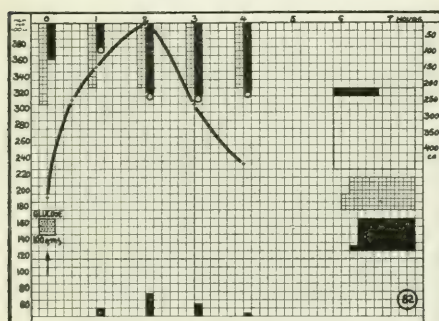
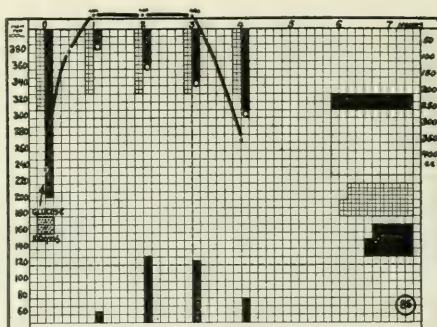
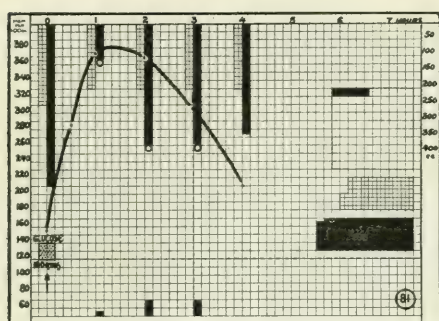


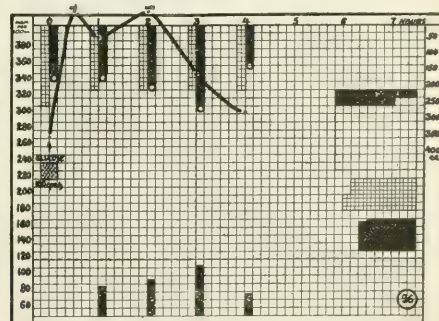
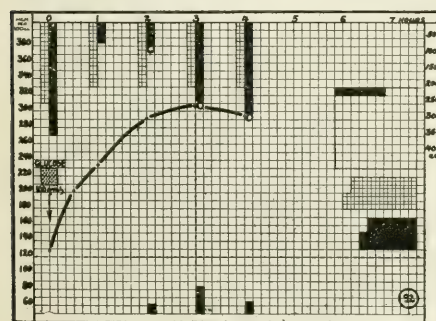
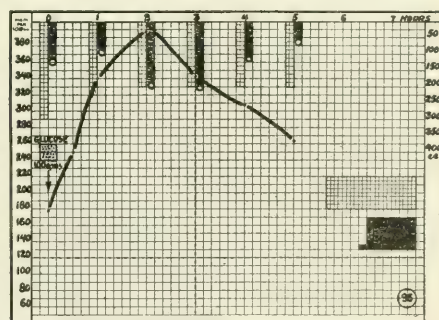
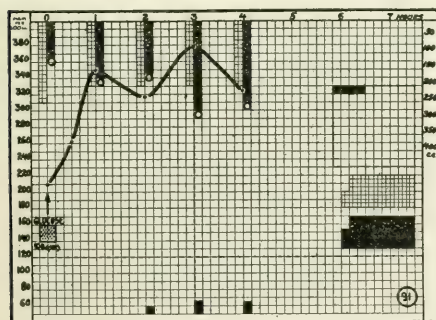
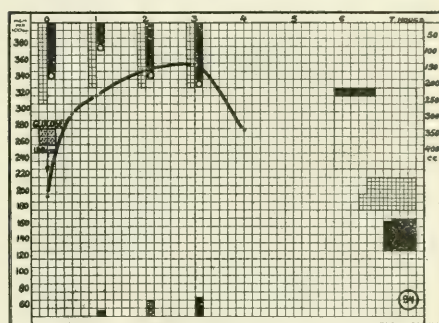
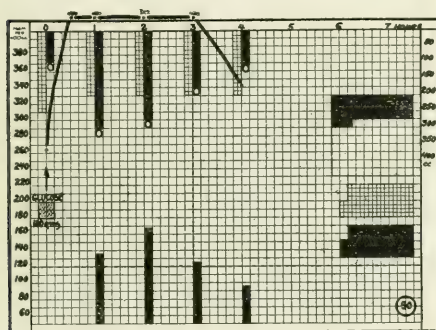
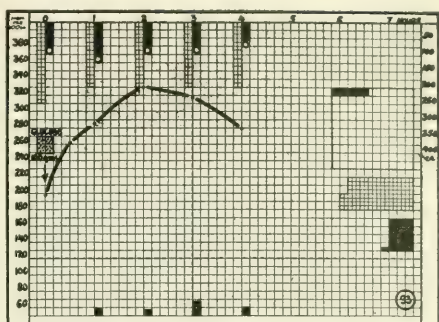
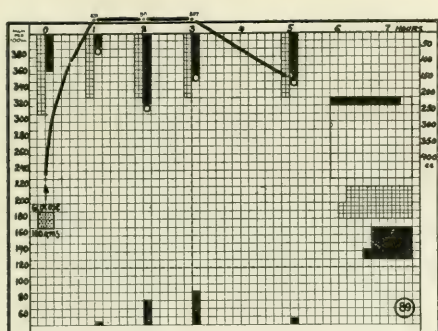


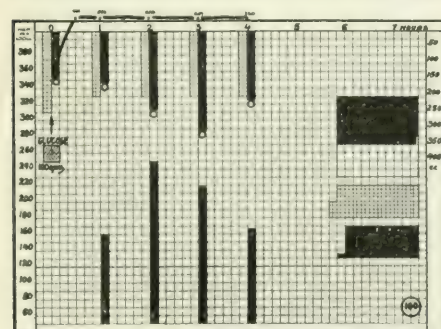
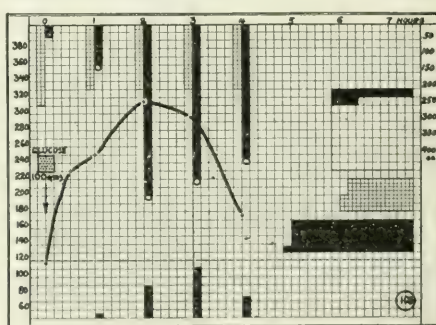
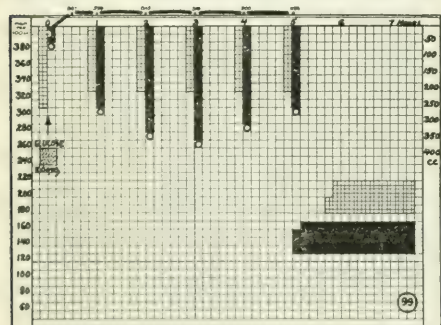
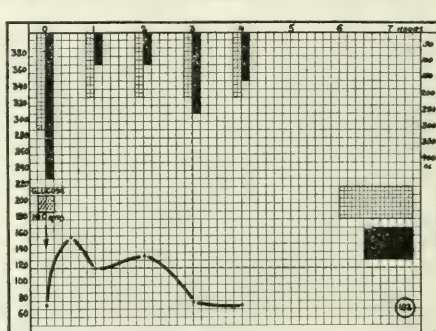
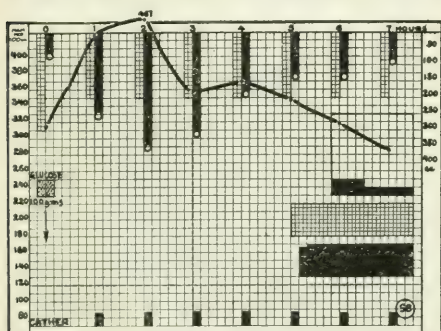
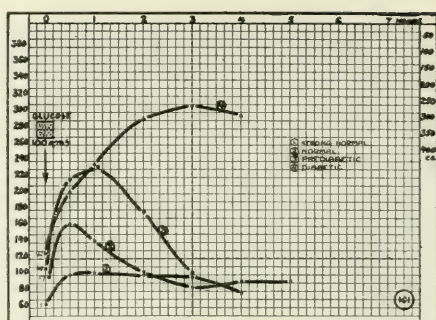
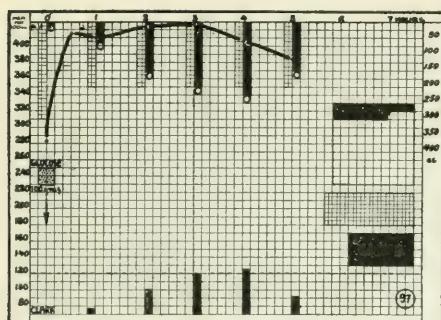












AN IMPROVED ALIMENTARY GLUCOSE TOLERANCE TEST

CAROL BEELER, B. S., Fellow in Chemistry,
ALBERT W. BRYAN, M. D., Fellow in Medicine,
EDWARD P. CATHCART, M. D., Fellow in Dermatology,
The Mayo Foundation, and
REGINALD FITZ, M. D., Section on Medicine, Mayo Clinic,
Rochester, Minnesota.

The perfection of clinical methods for blood sugar estimation has resulted in a number of reported observations on the effect on blood sugar concentration of a convenient dose of glucose administered by mouth. Hamman and Hirschman have introduced the method most often used in this country for making such studies. A fasting subject is given 100 gm. of glucose dissolved in water. The blood sugar concentration is estimated before the glucose solution is swallowed and later at intervals. Normal persons respond to such a dose of sugar by an increase in blood sugar concentration which usually reaches its maximum in about thirty minutes, returns to the normal level in sixty minutes, and remains at normal or below normal for several hours afterward. An atypical blood sugar curve suggesting lessened tolerance by this method has been reported in such different diseases as diabetes, nephritis, arteriosclerosis, rickets, cancer, disease of the liver, obesity, hyperthyroidism, arthritis and pituitary disease. The possible effect on the blood sugar curve of individual peculiarities in the absorption rate of the sugar solution from the intestinal tract in these various conditions has been discussed by several observers, notably, by Woodyatt, Sansum and Wilder, but has not been studied except by Fisher and Wishart in their work on dogs.

Woodyatt, Sansum, and Wilder have objected to the alimentary glucose tolerance test, and have devised an intravenous method which has not come into general usage, possibly on account of the technical difficulties involved. Their definition of glucose tolerance, however, is important. They believe that tolerance depends on the rate at which the tissues

are able to abstract a known amount of glucose from the blood by their combined powers to burn it, to reduce it into fat or to polymerize it into glycogen, and should be expressed as a velocity in grams of glucose for each kilogram of body weight for a unit of time. The present alimentary test can be modified to approach these requirements if the factor of absorption is taken into account.

In various textbooks of physiology it is asserted that sugar can be absorbed from the stomach in small amounts, but that it is rapidly absorbed from the intestine. In 1898, Zuntz called attention to the fact that sugar in solution in the intestinal tract of rabbits drew water to it so that the water content of the intestine was increased after the oral administration of sugar. Fisher and Wishart fed varying amounts of glucose to dogs, obtaining the blood sugar concentration and the sugar content of the intestinal tract at later intervals. They found a rapid though variable absorption of sugar from the stomach, and a more rapid and less variable absorption from the intestine. For example, in one experiment 50 gm. of glucose was given to a dog weighing 8.1 kg. An hour later the animal was killed. The stomach contained 5.6 gm. of glucose and the intestine 2.9 gm. In a second experiment the animal weighed 6.3 kg. and was given 50 gm. of glucose. Two hours later 11.1 gm. of sugar was recovered from the stomach and 1.7 gm. from the intestine. In a third experiment an animal weighing 7.6 kg. was given 50 gm. of glucose and two hours later the stomach contained 16.6 gm. of sugar while the intestine yielded only 1.0 gm. of sugar. Hence from these experiments it appears that the ingestion of sugar by an animal is followed by the entry of fluid from the body to the intestinal canal and by a variable absorption of sugar from it.

Nine persons without evident disease of the stomach were selected in order to determine whether the amount of sugar absorbed in an hour after a standard glucose meal was at all constant. This group consisted of four normal volunteers who were working in the laboratory and eating ordinary mixed diets, one obese patient, and four patients with diabetes. The patients were living on low carbohydrate and low calorie diets at the time the tests were made. Each person was given to drink slowly, after a previous fast of at least twelve hours, a solution of 100 gm. of pure anhydrous glucose in tap water

made up to a volume of 500 c.c. and flavored with lemon juice. The glucose was measured by weight. The temperature of the solution was not controlled. Each person took the sugar solution easily and none was nauseated.

During the sixty minutes after the sugar was ingested each person lay or sat still in a warm room. The gastric contents was then aspirated as completely as possible with a Rehfuß tube, the volume aspirated was measured and its sugar content titrated by Benedict's method. The small tube was used, since it has been shown by Rehfuß, Bergeim and Hawk that the stomach can thus be almost completely emptied. We were unable to control the amount of unabsorbed solution in the intestine at the time of aspiration, but assumed on account of the results of Fisher and Wishart that it was small, nor did we attempt to wash from the stomach the traces of sugar remaining after aspiration. The results of these experiments are found in Table 1.

TABLE I.

The amount of sugar recovered from the stomach one hour after standard glucose meal.

Case	Sex	Weight, kg.	Diagnosis	Glucose ingested, gm.	Glucose solution ingested, per cent	Fluid ingested, c.c.	Glucose in gastric content, gm.	Glucose in gastric content, per cent	Volume of gastric content
A.W.B.	M	89.5	Normal	100	20.0	500	29.0	8.3	350
F.R.	M	74.5	Normal	100	20.0	500	30.0	10.0	300
E.P.C.	M	65.7	Normal	100	20.0	500	26.8	6.7	400
E.C.M.	M	73.0	Normal	100	20.0	500	68.0	16.6	410
A188880	M	70.5	Diabetes	100	20.0	500	22.2	11.1	200
A279735	M	61.7	Diabetes	100	20.0	500	33.2	8.3	400
A381573	M	63.9	Diabetes	100	20.0	500	52.5	12.5	420
A382508	F	51.2	Diabetes	100	20.0	500	39.3	13.1	300
A380862	M	95.2	Obesity	100	20.0	500	30.8	7.7	400

The amount of sugar which was recovered in this fashion from each of the subjects was surprisingly large, very inconstant, and seemed to depend on individual idiosyncrasy rather than on any general law. However, each person ap-

peared to retain proportionately less sugar than water in the stomach; a finding which suggested a selective disappearance of sugar from the stomach with retention of water, or a dilution of sugar in the stomach by fluid drawn to it.

The view that a strong sugar solution introduced into the stomach is diluted shortly after ingestion was supported by the results in three experiments. The fasting stomachs of seven diabetic patients were emptied with the Rehfuß tube; while

TABLE 2

Fractional gastric analyses after standard glucose meal.

1. Case A289233, a man, weight 67.2 kg. Diabetes								
Time, minutes	Blood sugar mg. for each 100 c.c.	Hemoglobin, per cent	Glucose ingested, per cent	Volume ingested, c.c.	Glucose ingested, gm.	Glucose in gastric content, per cent	Volume of gastric content	Glucose recovered in gastric content, gm.
0	142	100	18.1	500	90			
3	144	100				17.2		
6	161	100				13.9		
10	181	100				12.5	500	62.5
2. Case A382688, a man, weight 57.7 kg. Diabetes								
0	121	123	20.0	500	100			
5	153	123				15.1		
10	175	123				16.1		
20	183					15.3		
30	227	114.5				14.2	445	63.2
3. Case A379705, a man, weight 62 kg. Diabetes								
0	118	84.0	19.1	500	95.5			
5						19.1		
10						18.5		
15	133	84.0				17.8		
20						18.5		
25						16.6		
30	200	84.0				16.6	365	60.6
4. Case A383397, a woman, weight 65 kg. Diabetes								
0	107	85.0	18.5	500	92.0			
10						18.5		
15	155	84.0						
20						18.5		
25						18.5		
30	222	80.0				16.6		
35						17.2		
40						16.6		
45						14.7		
50						14.7		
55						14.7		
60	235	79.0				14.7	350	51.4

TABLE 2 (continued)

5. Case A355591, a woman, weight 53.2 kg. Diabetes								
0	95		18.5	500	92.5			
10						8.53		
15	123					12.8		
20						13.9		
25						15.6		
30	192					15.1		
35						15.6		
40						15.1		
45	200					14.3		
50						13.9		
55						13.9		
60	224					13.5	466	62.9
6. Case A9984, a woman, weight 70 kg. Diabetes								
0	83	86.0	35.6	250	89.0			
10	106	97.5				3.4		
15						7.1		
20						10.0		
25						11.3		
30						12.5		
35						20.8		
40	169	93.1				21.6		
45						20.8		
50						21.6		
55						21.6		
60	240	93.1				19.2	250	48.0
7. Case A384253, a man, weight 54.1 kg. Diabetic suspect								
0	90	89.0	41.6	250	104.0			
10	90	89.0				22.2		
15						33.3		
20						31.2		
25						31.2		
30						29.4		
35						26.3		
40	142	89.0				25.0		
45						25.0		
50						27.2		
55						27.2		
60	142	89.0				15.6	420	65.5

the tube was still in place each patient swallowed a dose of glucose in a solution of variable strength prepared as in the previous experiments except that its sugar concentration was controlled by preliminary titration. A carefully mixed sample was aspirated from the stomach of each patient from time to time and titrated for its sugar concentration. Finally the stomach was emptied, the gastric content measured, and its sugar strength estimated. Blood samples, obtained from all

the patients before the sugar was ingested and at intervals later, were analyzed for sugar by the method of Folin and Wu, and for hemoglobin in all but one patient by the method of Palmer. The latter determination was made in order to detect any definite changes that might occur in blood volume. The results of these experiments are shown in Table 2. The findings in the first four cases were not particularly striking. The blood sugar percentage rose in each after the sugar solution was taken, the hemoglobin percentage fell in two, suggesting dilution of the blood, and all the individual gastric samples showed a consistent diminution in sugar concentration. The fifth patient reacted differently. The gastric content appeared to be rapidly diluted, as the sugar in a well mixed specimen withdrawn ten minutes after ingestion was 8.3 per cent. instead of 18.5 per cent. In later samples the sugar percentage gradually increased to 15.6 per cent., and finally fell to 13.5 per cent. Four hundred sixty-six cubic centimeters of fluid was removed from the stomach, or only 34 c.c. less than the volume ingested an hour previously, while 62.9 gm. of sugar was recovered instead of the original 92.5 gm.

A more concentrated sugar solution was used in the last two experiments. In the sixth the ingested sugar attracted fluid, as shown by the low sugar percentage of the gastric samples obtained, by the fact that there was a rapid immediate increase in hemoglobin concentration which later diminished, and because as much fluid was recovered from the stomach at the end of the experiment as was originally introduced. The seventh experiment differed slightly in that no change was discovered in the hemoglobin concentration, but one hour after the beginning of the observation 170 c.c. more fluid was recovered from the stomach than was taken.

The absorption rate of varying concentrations of sugar solution was studied. The results of these observations are recorded in Table 3.

Sugar in between 10 and 20 per cent. solution disappeared most rapidly from the stomach. As the sugar concentration of the solution was increased, the proportion of sugar retained in the stomach tended to become greater. When more dilute solutions were used, the rate of absorption seemed slower. There were, however, numerous individual exceptions to this general rule.

TABLE 3

The percentage of sugar recovered from the stomach after the ingestion of glucose meals of varying strengths

Case	Sex	Weight, kg.	Diagnosis	Duration of experiment, minutes	Glucose ingested, gm.	Glucose solution ingested, per cent	Fluid ingested, c.c.	Glucose in gastric content, gm.	Glucose in gastric content, per cent	Volume of gastric content	Per cent of ingested sugar recovered
A384253	M	54.1	Diabetic suspect	60	104.0	41.6	250	65.5	15.6	420	63
A381403	M	91.4	Diabetes	60	89.2	35.7	250	54.2	21.7	250	61
A9984	F	70.0	Diabetes	60	89.0	35.6	250	48.0	19.2	250	54
A382497	M	55.2	Diabetes	60	87.5	25.0	350	48.3	16.1	300	55
Average of nine cases in Table 1				60	100.0	20.0	500	32.5	10.5	300	32
A384400	M	73.8	Diabetes	60	82.5	15.0	550	27.0	10.4	260	33
H.O.P.	M	74.1	Normal	60	56.0	11.2	500	7.6	4.5	170	14
E.P.C.	M	65.7	Normal	60	59.5	10.9	500	14.6	6.1	240	25
A383421	M	66.0	Diabetes	60	50.0	10.0	500	10.9	5.9	185	22
A378767	M	47.0	Diabetes	60	50.0	10.0	500	3.6	2.4	150	7
A378767	M	70.7	Diabetes	60	50.0	10.0	500	Trace	Trace	57	Trace
A384007	M	74.6	Diabetes	60	52.8	7.0	750	13.2	5.0	265	25
A384241	M	82.6	Diabetes	60	50.0	6.6	750	19.8	6.6	300	40

We attempted to obtain data on the rate of absorption of glucose during shorter intervals in order to determine whether glucose was absorbed at a uniform rate or intermittently. For this purpose the stomachs of a group of patients were emptied at fifteen, thirty, forty-five, and sixty minute intervals after each had been given 500 c.c. of 20 per cent. glucose solution. We were unable to draw conclusions on account of the individual differences encountered, although it is probable that glucose is absorbed at a somewhat variable rate which depends in large measure on the concentration of sugar solution in contact with the intestinal wall at each unit of time.

The rate of entry of sugar to the blood does not entirely control the type of blood sugar curve which results from a glucose test meal, since the rate at which sugar is removed from the blood is also an important factor. This is shown by Figures 1, 2, and 3.

In the normal individual (Fig. 1) the peak of blood sugar concentration was reached in about thirty-five minutes after the glucose had been ingested; it was returning toward normal at the end of an hour. The stomach at this time contained

27 gm. of glucose, or 400 c.c. of 6.7 per cent. glucose, which was certainly a sufficient amount to affect the blood sugar concentration during its absorption. There is no reason for suspecting that absorption had ceased. The fall in blood sugar concentration was not accompanied by a change in blood volume great enough to influence the hemoglobin concentration. Therefore, the conclusion seems justified that at the onset entry of sugar to the blood was more rapid than withdrawal of sugar from the blood; when the peak of blood sugar concentration was reached entry of sugar to the blood and withdrawal of sugar from the blood were equal; finally although entry of sugar to the blood continued, withdrawal of sugar from the blood was more rapid and as a result the blood sugar concentration lessened.

In the diabetic patient (Fig. 2) the same process occurred except that the withdrawal of sugar from the blood at the end of an hour was only rapid enough to hold the blood sugar level and was not great enough to diminish the blood sugar concentration. This may have depended on the fact that the initial rate of absorption was slower than in the first case, as is suggested by the large amount of sugar recovered. In any event when absorption was stopped by emptying the stomach, withdrawal of sugar from the blood continued and the blood sugar concentration fell toward normal.

In the diabetic patient (Fig. 3) the blood sugar concentration continued to rise after absorption had stopped. This finding can be explained on the ground that sugar continued to enter the blood from the intestine after the stomach was emptied. On the other hand, the reaction was so different from that of the other cases as to suggest that while absorption of sugar from the intestine may have been a factor in the findings, yet the main cause of the continued hyperglycemia lay in a defective withdrawal mechanism. Maclean and de Wesselow, confirming Langfeldt's experimental work, have made comparable observations in their studies on glucose tolerance in diabetics.

We believe that the usual alimentary glucose tolerance test can be improved by taking these various facts into consideration, and have used it satisfactorily in the following manner: A fasting subject is given to drink a known amount of glucose dissolved in water. The ingested solution contains not more than 20 per cent. of glucose in order to secure good absorption

and the volume is limited to 500 c.c. since it is difficult for most persons to drink rapidly a larger quantity of fluid. An hour later the stomach is emptied as completely as possible and the amount of recovered sugar is determined. The difference between the amount recovered and the amount ingested, measures, with a small error, the amount absorbed. This is expressed as grams of sugar absorbed for each kilogram of the subject's weight for each hour of time. Blood sugar and hemoglobin determinations are made before the glucose is ingested, at the time the stomach is emptied, and at later intervals.

Since the amount of absorbed sugar and the resultant hyperglycemia vary in each case, we have attempted to make the results in one case comparable to others in the following way. The blood sugar readings are corrected for any demonstrable blood volume change and for the variable amounts of sugar which have been absorbed. The first correction is made from any changes found in the hemoglobin percentage. The second correction is made from the relationship between the amount of absorbed sugar and the degree of glycemia found. The results are made uniform by estimating from these data the proportional blood sugar readings which would have been obtained under the conditions outlined had 0.800 gm. of glucose for each kilogram of weight of each subject been absorbed. This dosage of glucose was selected because Wilder and Sansum found that it represented the upper limit of normal glucose tolerance for an hour by the intravenous method in human subjects.

We recognize that this method of interpreting the results is open to criticism since it is not justified by experimental evidence. We have employed it, however, as a matter of convenience in an attempt to obtain the probable effect on the blood sugar of a known and constant amount of glucose absorbed during a known time interval, to follow the rapidity with which the hyperglycemia so induced disappears after absorption has ceased, and to make the result from one case directly comparable with the results from others by introducing a factor common to all. The information obtained this way at least is more definite and accurate than if none of the possible variables are considered and makes the test approach the standard in a sugar tolerance test demanded by

Woodyatt, Sansum, and Wilder. A few typical results are recorded in Table 4.

TABLE 4

The results of a series of alimentary glucose tolerance tests

Case	Diagnosis	Glucose absorbed for each kg. each hour	Blood sugar mg. for each 100 c.c.							
			Readings obtained by analysis				Estimated readings obtained if 0.800 gm. glucose for each kg. each hour had been absorbed			
			1 Before ingestion of glucose	2 1 hour later	3 1 hour after absorption checked	4 2 hours after absorption checked	1 Before ingestion of glucose	2 1 hour later	3 1 hour after absorption checked	4 2 hours after absorption checked
H.O.F.	Normal	0.65	97	106	90	90	97	120	111	111
R.F.	Normal	0.94	107	153	80	90	107	130	68	77
A385046	Renal diabetes	0.74	121	140	66	77	121	151	71	83
A359458	Suspected diabetes	1.06	117	284	127	82	117	214	96	62
A188880	Mild diabetes	1.10	100	270	181	90	100	196	132	65
A385075	Mild diabetes	0.49	117	166	105	100	117	270	171	163
A384400	Severe diabetes	0.65	147	400	317	277	147	492	392	400
A382237	Severe diabetes	0.71	192	444	339	332	192	500	384	373

SUMMARY

Clinical observations made to emphasize certain obvious defects in the alimentary glucose tolerance test as it is now generally performed are reported. Such defects have been discussed by others but have not received sufficient attention.

The absorption of glucose from the intestinal tract is a complicated physiologic process. The rate of absorption varies in each individual within wide limits. The factors which control the rate of absorption are uncertain beyond the fact that a glucose solution of about 10 per cent. concentration

tends to disappear more rapidly from the stomach than solutions of greater or less concentration, and that concentrated glucose solution in the stomach often attracts fluid. Whether or not the rate of absorption of sugar is uniform, what effect temporary variations of the rate of absorption have on the blood sugar curve, and what effect abnormalities in gastric function have on the rate of glucose absorption, have not been discovered. It is obvious, however, that since the rate of entry of glucose to the blood is an important factor in determining the type of resultant blood sugar curve and since it is variable and cannot be controlled, all results from the present alimentary glucose tolerance test are open to criticism.

The rate at which sugar leaves the blood after a known amount of glucose has been absorbed, on the other hand, is a second important factor in determining the resultant blood sugar curve. It can be estimated with a fair degree of accuracy. Normally, the disappearance time of alimentary hyperglycemia after absorption has ceased is very rapid. In conditions of diminished glucose tolerance the hyperglycemia persists for varying lengths of time, the duration of hyperglycemia and the degree of intolerance being fairly parallel.

A simple modification for the present test is suggested which takes these facts into consideration, which avoids as far as possible the variable factor of absorption, which emphasizes the duration of hyperglycemia after absorption is checked, and which makes results from one case directly comparable with those obtained in other cases.

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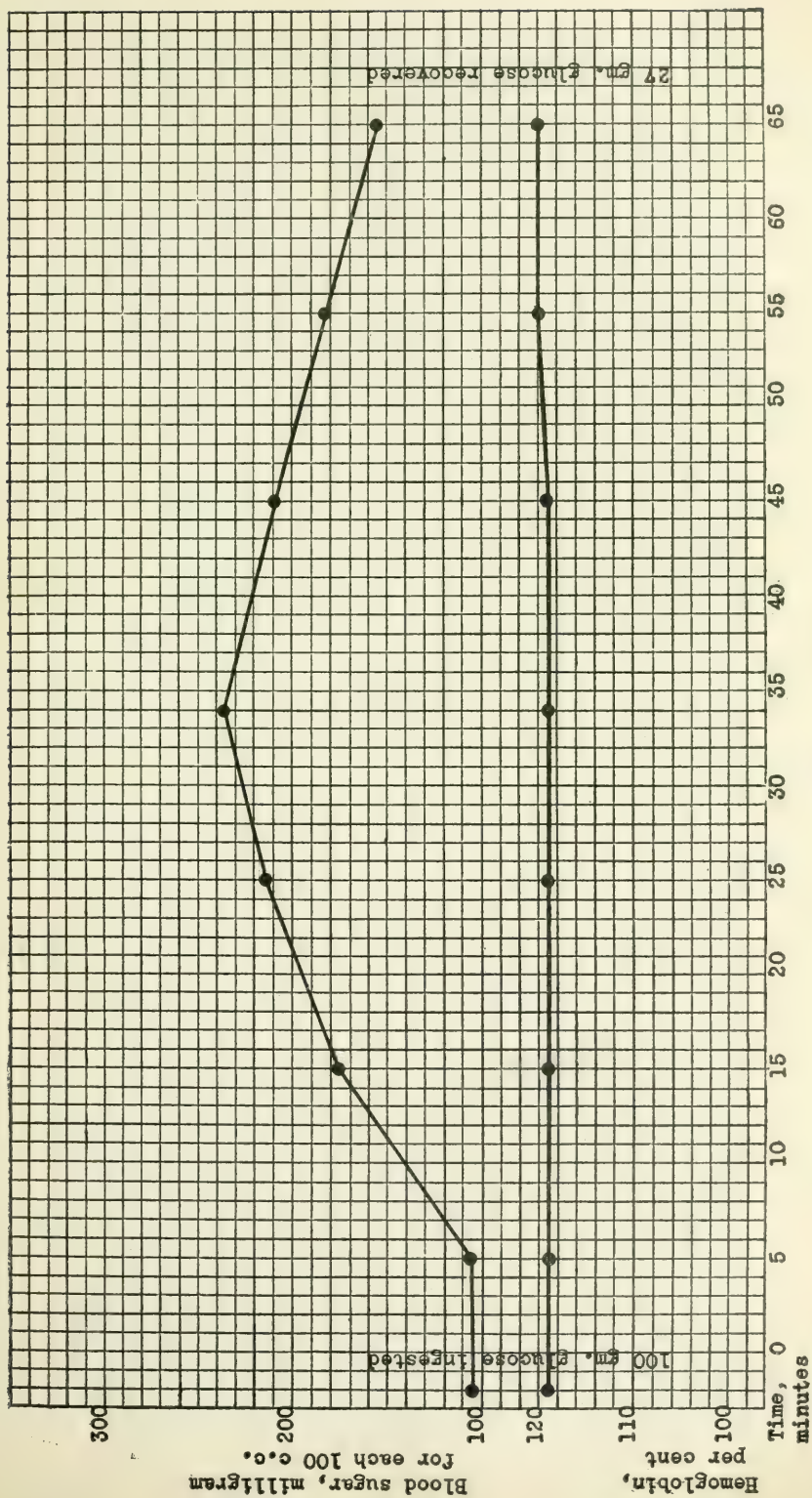


Fig. 1. Case 1. Normal.

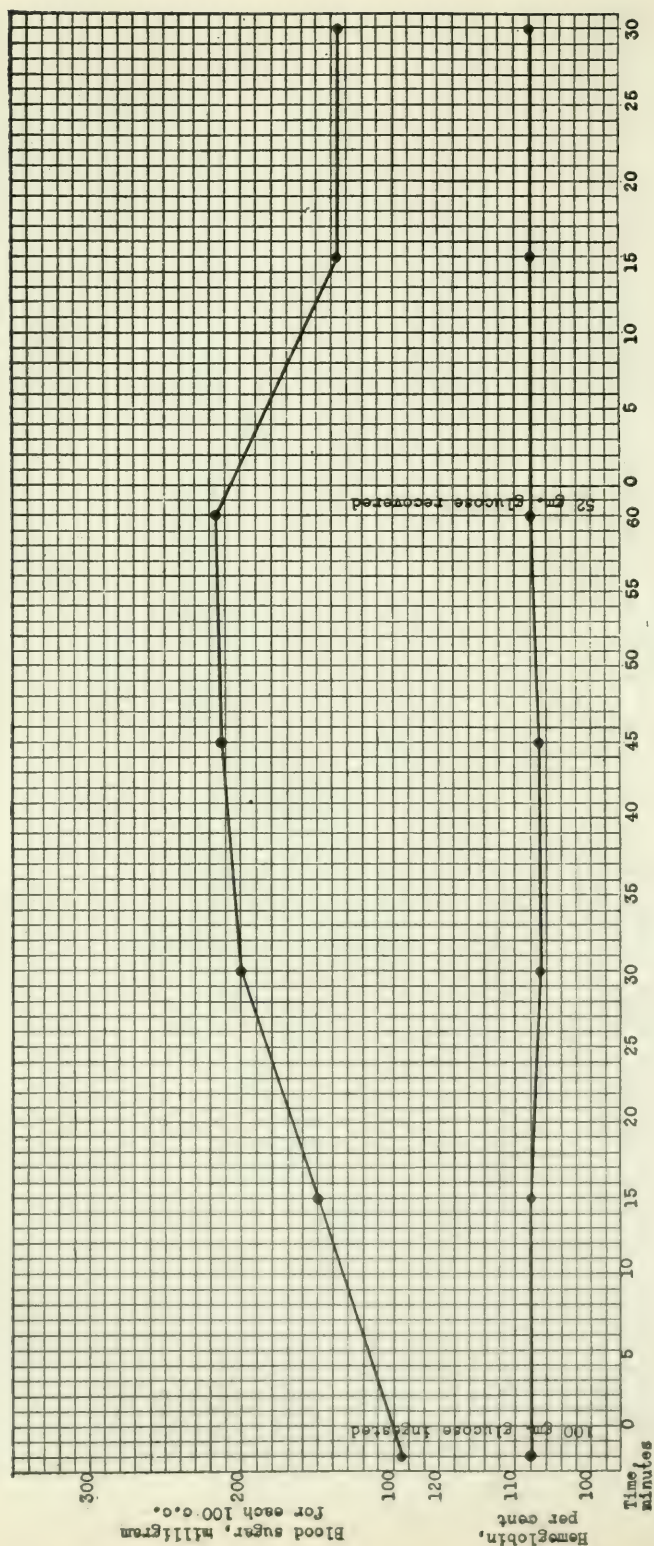


FIG. 2. Case 2. Mild diabetes.

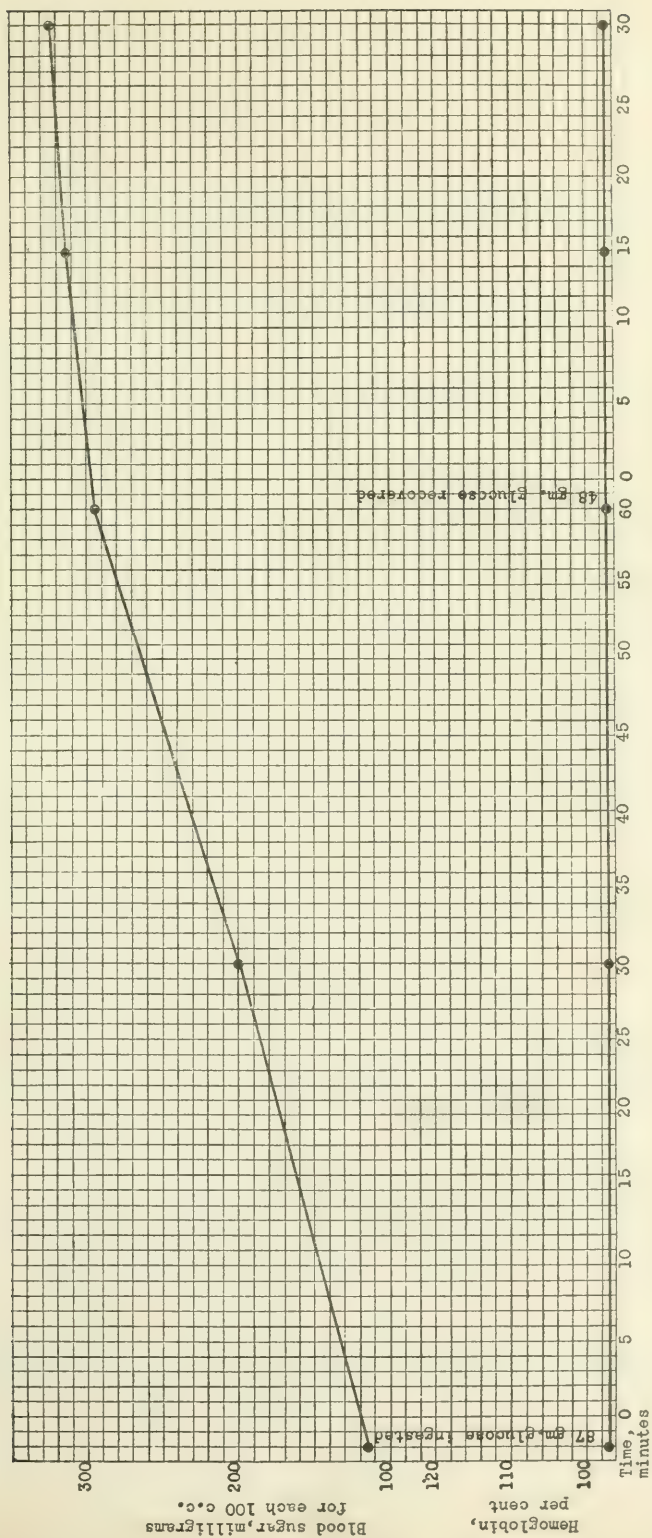


FIG. 3. Case 3. Severe diabetes.

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THE TRANSFORMATION OF PROTEIN INTO FAT AND FAT INTO CARBOHYDRATE IN THE BODY*

BY HARRY VICTOR ATKINSON, B. S.

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* Thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmacology in the Graduate School of the University of Illinois, 1922.

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I. INTRODUCTION

There are nine transformations which the three common foodstuffs, fat, carbohydrate, and protein, may undergo in the body. The three simplest transformations are known to take place and are no longer the subject of controversy among physiologists. They are:

1. Food fats into tissue fats.
2. Food carbohydrates into tissue carbohydrates.
3. Food proteins into tissue proteins.

The next two transformations are more complex, but the fact that they do take place in the body is well established. They are:

4. Food proteins into tissue carbohydrates.
5. Food carbohydrates into tissue fats.

Claims are put forth that two other transformations can take place, but the preponderance of the evidence is to the negative in the bodies of higher animals at least. They are:

6. Food fats in the presence of some simple source of nitrogen into tissue proteins.
7. Food carbohydrates in the presence of some simple source of nitrogen into tissue proteins.

The last two transformations have long been the subject of dispute. They are:

8. Food proteins into tissue fats.
9. Food fats into tissue carbohydrates.

This investigation is concerned principally with the last two disputed transformations, but since all these transformations are so inter-related in their intermediary metabolism, it seems necessary to discuss the others briefly.

1. Transformation of Food Fats into Tissue Fats.

Every food fat ingested is saponified in the alimentary tract, absorbed as a soap and re-combined into a fat in the intestinal wall. When

small amounts of fat are fed, the fat deposited in the tissues is characteristic of the species, but when larger quantities of a fat such as mutton tallow are fed, the tissue fat may have the melting point of the particular fat for a short time, but ultimately the tissue fat becomes characteristic of the species¹.

2. Transformation of Food Carbohydrates into Tissue Carbohydrates.

Physiologists agree that every digestible carbohydrate, no matter whether it be starch, glucose, galactose, or levulose, is changed in the normal animal to glucose and deposited as glycogen.

3. Transformation of Food Proteins into Tissues Proteins.

No matter what kind of a protein be fed it is broken down into amino acids in the normal organism and either destroyed or re-built into tissue proteins characteristic of the species. The best evidence of this transformation is the experiments of Abderhalden and Samuely² who gave to a horse 1500 gm. of gliadin, a protein containing four times as much glutamic acid as the serum proteins present in the blood, and found no change in the composition of these proteins.

4. Transformation of Food Proteins into Tissue Carbohydrates.

Pflueger³ fed a large amount of codfish to a fasting dog and found as much glycogen in the liver as would have been deposited after excessive carbohydrate feeding, thus proving the formation of glycogen from the protein of the codfish.

It is an accepted fact that the phlorizinized dog and the diabetic man can transform about 58 per cent. of the protein molecule into glucose. The normal dog can also build carbohydrate from protein, as shown by Williams, Riche and Lusk⁴, who gave 1200 gm. of meat to a dog and made observations in hourly periods upon the nitrogen in the urine, the carbon dioxide eliminated, the oxygen absorbed, and the heat produced. They found that, beginning with the second hour and continuing for fourteen hours after the ingestion of protein, the respiratory carbon dioxide was less than that which one would expect had all parts of the protein complex been oxidized. There was, therefore, carbon retention during this period. This carbon they found to be retained in the form of carbohydrate. They calculated the oxygen consumption on the hypothesis that this carbon had been retained as glucose, and found that it agreed within 0.9 per cent. of that actually determined in the experiment. When they calculated the oxygen required, had the carbon been retained as fat, they found a difference of 10 per cent. They also found a falling respiratory quotient (below that of protein itself) which would indicate that the carbon was retained as glycogen. A rising respiratory quotient would indicate that it had been retained as fat.

5. *Transformation of Food Carbohydrates into Tissue Fats.*

Weinland has shown that ferments, expressed from living ascaris, convert glycogen into glucose and this into valerianic and possibly caproic acids.^{5a, b, c}

Definite proof of the conversion of carbohydrates into fats was also furnished by Meissl and Strohmer⁶ for the pig; Voit and Lehman⁷ for the goose and Rubner⁸ for the dog.

When this transformation takes place in the organism, the respiratory quotient which is the ratio of the $\frac{\text{Volume CO}_2 \text{ produced}}{\text{Volume O}_2 \text{ absorbed}}$ may be considerably over unity. The reason for this is that an oxygen rich substance is being converted into fat, which is poor in oxygen. Hence, the volume of the carbon dioxide produced may be greater than the volume of the oxygen consumed. Thus Bleibtreu⁹ found a respiratory quotient of 1.33 on feeding a goose with much grain, although the same goose had a respiratory quotient of 0.728 when fasting. Pembrey^{10a} found that a marmot, after eating much carbohydrate previous to hibernation, had a respiratory quotient of 1.39. In addition to these facts the fattening qualities of starchy foods are well known.

6. *Transformation of Food Fats, in the Presence of Some Simple Source of Nitrogen, into Tissue Proteins.*

In a mixed diet fat has less protein sparing action than carbohydrates and I know of no evidence that it can form protein, either in lower animals or in mammals, in the presence of a simple form of nitrogen.

7. *Transformation of Food Carbohydrates, in the Presence of Some Simple Source of Nitrogen, into Tissue Proteins.*

Tubercle bacilli¹¹ and yeast cells¹² have the power to synthesize protein from sugar and some simple source of nitrogen, and this power has also been claimed by Grafe¹³ for higher animals. This synthesis is denied by Abderhalden.¹⁴

II. TRANSFORMATION OF FOOD PROTEINS INTO TISSUE FATS.

It is known that protein, under some conditions, can form glucose and glucose fat; therefore, one is apt to assume that ingested protein forms fat. While this conclusion is quite correct, as shown by my own experiments, the method of reasoning is, in my opinion, fallacious because the reaction within the body is not through the intermediate formation of glucose.

HISTORICAL.

Hoppe-Seyler¹⁵ in 1856, gave to a dog a diet of sugar alone, of meat alone, and then a mixed diet of meat and sugar. He found that, after

allowing for the nitrogen of the meat, less urea was eliminated on the mixed diet; and this diet caused a gain in weight which he interpreted as due to fat production, but which Taylor¹⁶ points out might have been due to water retention. The experiment did not prove the production of fat from protein, but did illustrate the protein sparing property of carbohydrates.

Voit and Pettenkofer^{17a} at Munich, in 1862, placed a 34 kilogram dog which had been fed 1500 gm. of meat, freed from fat, daily for 25 days in a respiration-calorimeter. The respiratory exchange, and later nitrogen eliminated were determined. They found that all the nitrogen was eliminated, but a part of the carbon retained. This retention they considered to be in the form of fat; it was too great to be in the form of glycogen. Their conception was that the protein molecule was broken up into a nitrogenous and a non-nitrogenous moiety. The nitrogenous moiety was largely the precursor of urea, and a part of the non-nitrogenous moiety was retained as fat. They thought nearly all the body fat was derived from proteins, directly or indirectly. They cited the formation of fat from the degeneration of cells in phosphorus poisoning, adipocere formation, and the ripening of cheese, to support their claims. Evidence is presented later which indicates that in none of these cases is there a fat formation from protein. The work of Voit, Pettenkofer and their co-workers, and the teachings of Virchow¹⁸ and Klebs¹⁹ seemed to settle the matter until this work was criticized by Pflueger^{20a} in 1892.

As a result of a study of the source of muscle energy, Pflueger^{20a} contradicted Voit's theory of the formation of fats from protein. He demonstrated, and it was later admitted by Rubner^{21a} and Cremer^{22a}, students of Voit, that the ratio of carbon to nitrogen, 3.68 to 1, used by Pettenkofer and Voit was too high. Voit had not analyzed the meat which he fed his dogs, but calculated the nitrogen and carbon content on the basis of what are now known to be incorrect analyses. He assumed a nitrogen content of 3.4 per cent., or 14.1 per cent. nitrogen in the dried residue, which is low. He also assumed a carbon content of his dried protein of 52.0 per cent., which is higher than in most proteins. The relation of carbon to nitrogen (3.68) was therefore too high. Voit had also assumed that all of the carbon and nitrogen of the meat were in the form of protein, and it is now known that there are some extractives in muscle rich in nitrogen (creatine, urea) which are eliminated unchanged (23). Some muscle also contains more glycogen and fat than Voit supposed, which might have been stored in the dog, thus giving a carbon retention. Pflueger's^{20b} recalculation showed that carbon retention was either absent or very slight. Even though the fat formation had occurred, it might have been from glycogen or fats in the diet used. Pflueger also pointed out that although Voit's figures showed a urinary nitrogen balance, there was at the same time a marked increase in weight of the dogs which was contrary to his own extensive experiments. This confirmed, in his opinion, the fact that Voit had estimated the nitrogen of his diet too low and that the dogs had retained nitrogen as well as carbon.

Pflueger pointed out other questionable factors; the small quantity of water given to the animals might lead to a retention of nitrogen, and the method of Liebig which was used for the determination of urea, he regarded as faulty. Pflueger thus clearly showed that Voit had not demonstrated the production of fat from protein in the dog and later experiments confirm Pflueger's claims. It will be shown that 1500 gm. of meat per day fed by Pettenkofer and Voit to a 34 kilogram dog is not sufficient to cause fat production; however, if Voit's dog had taken twice this amount of proper protein, and had his apparatus been sufficiently accurate to show hourly fluctuations in metabolism, he would have obtained evidence of this conversion.

C. Voit's brother, Erwin²⁴, repeated the experiment in 1892 and employed the C:N coefficient of 3.2 for proteins. Rubner²¹, working in Voit's laboratory showed that the C:N coefficient 3.68 for protein was inaccurate, and that meat fully extracted with ether contains only 3.28 gm. of carbon to one of nitrogen. Erwin Voit and Rubner admitted that in C. Voit's earlier work it was an error not to have analyzed the meat and to have concluded that a gain in weight was a gain in fat. E. Voit fed a 23 kilogram dog with 1500 gm. of meat daily for three days and found a slight carbon retention which he attributed to fat formation and not to glycogen formation "because that was not probable." Taylor¹⁶ considers these experiments inadequate and raises many objections to the method employed and considers that the formation of glycogen was not excluded. This amount of meat fed to a 23 kilogram dog is hardly sufficient to cause fat formation.

Cremer²² reinvestigated the subject by starving a cat and then giving the animal about 450 gm. per day of lean meat, or three times the normal diet. He collected the total excretions. The carbon belonging to the meat ingested was calculated at the low ratio of 3.18 to 1 of nitrogen. During eight days there was a daily retention of 7.3 gm. of carbon or 58.4 gm. in all, or 17.5 per cent. of the total protein carbon, corresponding to a glycogen production of 130 gm. The cat, however, contained only 35 gm. of glycogen as determined by the analysis of the dead animal at the end of the experiment. The muscles contained 1.47 per cent. of muscle glycogen, which is higher than E. Voit²⁴ found in geese after carbohydrate ingestion (maximum 1.37 per cent., Voit).

Taylor¹⁶ objects to the unproven statement of Cremer that his meat was free from fat and glycogen, also to Cremer's failure to determine how much food lay in the digestive tract at the end of the experiments. Taylor, in a critical review of the subject of fat production from protein in 1899, states that the formation of fats from protein physiologically or pathologically had not been demonstrated. Pflueger²⁰ also claims as does Taylor that fat formation from protein still remains unproven. However, the author of this thesis regards Cremer's evidence as sufficient to prove the formation of fat from protein in the cat.

Subbotin²⁵ fed fasted dogs on pure meat and pure forms of fat; one had meat with palmitin, and another meat with an olein-free soap. He found stearin and olein deposited in the body and concluded in-

correctly that these must have come from the proteins of the diet, since the dog and the diet were supposed to have been free of fat and glycogen, except for the palmitin and olein ingested. These experiments simply proved that the dog could re-form its own type of mixed fat from palmitin or olein. There is reason to believe that the dog was not freed of its carbohydrates or its stored-up fats by starvation, and the period of starvation was not long enough.

Ssubotin²⁶ fed bitches on a meat diet and found more fat in the milk than when the same animals were fed a mixed diet, and Kemmerich²⁷ found that the fats in the milk might exceed the fats (not fats and carbohydrates) in the diet. Voit²⁸ admitted that if the fats in the milk could come from body fats, the above experiments would not prove the conversion into fat, but declared it improbable, although he did not attempt to disprove it. Rosenfeld²⁹ later showed that the fat of the milk in these conditions does in fact come largely from body fats.

III. FATTY INFILTRATION AND DEGENERATION.

The earliest ideas of the formation of fat from protein were due largely to the teachings of Virchow¹⁸ who divided the fatty changes that may occur in pathological conditions into two groups, "infiltration" and "degeneration". By the former he indicated a condition in which body fat passed from one cell into another, but with little damage to cell structure. By the latter, fatty degeneration of protoplasm, he indicated a condition of fine droplets and cellular disintegration not accompanied by transportation of fat. Virchow considered the cell fat in this latter condition to be derived from cell protein. This pathological evidence will be reviewed and it will be shown that in fatty degeneration there is no increase in the total amount in the cell, but that its physical state only is changed. Chemical analysis even in the most pronounced cases shows no increase in the total fat content.

IV. PHOSPHORUS POISONING.

There is an increase in the fat content of the liver after phosphorus poisoning. The claim has been made that this fat is derived from protein. Lebedeff³⁰ investigated this phase of the question by stuffing a lean dog for several days with meat and linseed oil. He then poisoned it with phosphorus and killed it after several days. The typical fatty liver of phosphorus poisoning was found and more than one-half the fat had the properties of linseed oil. Since fat is not absorbed through the portal circulation, it could not have lodged in the liver at the time of its absorption.

A considerable proportion of the fat of the body is derived from fat in the food. Rosenfeld²⁹ proved this by feeding sheep fat to a starved dog. The dog was again starved and the ingested fat was found deposited as sheep fat in the dog's adipose tissue. When phosphorus or phlorizin poisoning was induced and the liver examined, 40 per

cent. of the fat in the liver was found to be sheep fat and not dog fat, which it should have been if formed by degeneration of cell protein. In addition, he found that the liver had lost little of its nitrogen. Therefore, fat was simply transported to the liver from the fat deposits of the body. He confirmed these results by feeding linseed oil and subjecting the animal to similar treatment.

Rosenfeld^{29c} also showed that when starved chickens were poisoned with phosphorus they did not present a fatty liver, while chickens in good nutrition did so. He then studied the production of fat from protein by fattening a starved bitch with sheep fat. She lost her pups before term, but gave a good secretion of milk. The fat in her milk was mutton fat. In this series of experiments Rosenfeld proved by means of phlorizin and phosphorus, and milk production, that the fat was derived not from proteins but from body fats, i.e., the process was infiltration and not degeneration.

Bauer³¹ analyzed the tissues of animals poisoned with phosphorus and found the fat content to be above normal. Since Storch³² had found an increase of urea in connection with phosphorus poisoning Bauer reasoned that the fats had been formed from disintegrated proteins. This conclusion was not warranted because the fat in local areas of the pieces of tissue selected could have been an infiltration and the total fat of the body not increased, which was proven later by Shibata³³.

Taylor¹⁰ quotes the experiments of Monaco³⁴ who showed that the respiratory exchange of mice poisoned with phosphorus was not decreased, and the urinary nitrogen was but little increased. These results were in direct contradiction to those of Bauer.

In order to rule out some of the local changes of tissues at the expense of other more or less distant tissues, Leo³⁵ used small animals which could be poisoned and analyzed entirely. He used young guinea-pigs which he first fasted for five days, and then poisoned some with phosphorus; all were killed on the third day. The poisoned pigs contained much more of lipoidal material soluble in ether than those unpoisoned. He treated frogs in the same way and confirmed the guinea-pig results, but obtained opposite results on rats. Leo concluded that fat was produced from protein in phosphorus poisoning, and the contrary results in rats he explained by assuming that there had been an excessive combustion of fat, but offered no proof. However, he did not use animals of the same sex, which is especially important in frogs, since Polimanti³⁶ found more fat in females than in males. It was in frogs that Leo obtained his most striking results; but he did not exclude fat formation from glycogen. His analytical methods have also been criticized¹⁴. However, he did find that the lecithins were not increased, thus disproving Hoppe-Seyler's¹⁵ idea that it was from the lecithins that fats were indirectly derived from proteins.

Schmidt³⁷ investigated fat production in phosphorus poisoning by using starved pigeons. He found less fat in the poisoned pigeons than in the controls.

Polimanti³⁶ poisoned male frogs and reported an increase in total fat. Since the animals were starved he assumed that they contained little glycogen; therefore, he concluded that fat had been formed from protein; but Pflueger showed that frogs contain more glycogen than was necessary to account for the increase in fat found by Polimanti in frogs, and this destroyed the validity of Polimanti's conclusions.

In 1911 Shibata³³ investigated this problem by determining the nitrogen and the fat content of livers and also of the remainder of the bodies of mice which were (1) normal; (2) starved; (3) starved and poisoned with phosphorus; (4) fed with bread and poisoned with phosphorus. He states that if fasting mice are poisoned with phosphorus, fat is transported to the liver from subcutaneous fat. Increase of the fat of the liver is accompanied by a decrease of body fat. Furthermore, cod liver oil injected subcutaneously in phosphorized mice is transported to the liver, where it can be recognized by its high iodine number and low melting point. Oil injected in non-poisoned, fasting mice was not absorbed to any appreciable extent. In fasting phosphorized mice and frogs, a loss of body nitrogen occurs, but no greater than was occasioned by fasting alone. Furthermore, he found that animals starved to an extremely low fat content did not develop the typical liver of phosphorus poisoning, a fact previously noted by Lebedeff³⁰. All Shibata's evidence is entirely against the supposition that fat is formed from body protein.

Additional evidence is the fact found by Leathes³⁸, Hartley and Mavrogordato³⁹, Jackson and Pearce⁴⁰, that in fatty human livers the iodine number, normally high, falls as the amount of fat increases until it is approximately that of adipose connective tissue. Further evidence as to the transportation of fat is that of Schwalbe⁴¹ and of Wells^{42b}, who have shown that the iodine compounds of fat are transported into fatty organs of animals subjected to phosphorus poisoning.

Lusk⁴³ states that in fatty "degeneration" of the liver, phosphorus poisoning and acute yellow atrophy of the liver, the lactic acid disappears from the blood and urine if phlorizin glycosuria be induced, as shown by Mandel and Lusk⁴⁴. Lusk believes that the lactic acid is derived from sugar formed in protein metabolism. In the case cited the sugar is removed without conversion into lactic acid. In phlorizin glycosuria, glucose does not burn; in phosphorus poisoning lactic acid derived from glucose does not burn. In both cases a sugar hungry cell, or one in which carbohydrate is not oxidized, is found and under these circumstances fat is attracted to the cell in larger quantities than can be utilized.

Lusk states that wherever sugar freely burns this fatty infiltration is impossible. In corroboration he cites the fact that Rosenfeld^{29c} found 10 per cent. of fat in fasting liver. If carbohydrate, or protein which yields carbohydrates on metabolism be ingested, the fat content decreases to 6.2 per cent. If fat be given to a fasting dog, the liver may contain 25 per cent. of fat, but if carbohydrate be ingested at the same time, the fat is deposited elsewhere. Thus there is an anta-

gonism in the liver between glycogen deposit following carbohydrate ingestion and fat deposition.

Lusk points out also that a reduced local circulation in a portion of the heart may produce anemia of the part, a reduced local oxidation of the lactic acid normally found, and a fatty infiltration of the locality. He offers this hypothesis to explain the fatty changes in tissues.

According to Wells⁴² there may be fatty degeneration without infiltration. By showing that new fat in fatty livers is infiltrated fat, Rosenfeld^{29e} did not determine the source of the fat found in the cells under such pathological conditions. In the course of his analyses of organs that were macroscopically or microscopically the seat of fatty degeneration he found that there is not always a relationship between the amount of fat that seems to be present as determined by microscopic methods, and the amount actually found by chemical analysis. This is particularly true of the kidney. Thus, the amount of lipin found to be present in normal kidneys (dogs') is, on the average, 21.8 per cent., whereas after producing a typical fatty degeneration by means of phosphorus and other poisons, the lipins were never found to be increased. He concluded that microscopic examination gives no indication of the amount of fat contained in a degenerated kidney, since a pathologic kidney showing extreme fatty degeneration under the microscope may contain no more lipins than a normal kidney which may not show any fat whatever by staining methods.

Every tissue may contain a greater or less amount of lipin which can not be stained by any stains available for the purpose (Wells). Neither can all of the fat in tissue be extracted by means of a simple solvent such as ethyl ether or petroleum ether. This resistance to extraction is not a mechanical or physical phenomenon, because the tissue may be pulverized to the finest consistency and extracted in a variety of ways, yet a portion of the fat can not be extracted (Pflueger and his pupils). This resistant fat seems to be essential to the cell, for it can not be removed by extreme starvation. It is not a simple fat but lecithin, cholesterol and other compounds, as indicated by Bondi⁴⁵ who has shown that fatty acids can combine with amino-acids to form "lipo-peptids," very similar in their properties to these "masked fats." However, digestion with hot alkali, pepsin, papain or pancreatin frees the fixed fats so that they can be readily extracted with ether. But when pathological changes in the cell result in decomposition of the cell protein, the "invisible lipin" is set free and, becoming visible, produces the so-called "fatty degeneration" [Klemperer⁴⁶, Bell⁴⁷, Wells^{42a}]. This explains the observation of Rosenfeld that macroscopic and microscopic methods may show much fat when tissues actually contain even less than normal amounts. Taylor¹⁴ showed that during fatty degeneration in phosphorus poisoned frogs this combined fat is liberated and becomes ether soluble. Mansfield⁴⁸ also found that in animals poisoned with phosphorus the proportion of fat, which is present in a form free from protein combination in both blood and viscera, is increased, while firmly bound fat is decreased. Organs undergoing experimental autolysis show microscopic-

ally an apparent typical fatty degeneration, although analysis shows that no actual increase in fat occurs (Dietrich⁴⁰, Hess and Saxl⁵⁰, Ohta⁵¹, and Shibata⁵²). Bainbridge and Leathes⁵² found that after ligation of the hepatic artery there is a marked fatty degeneration of the liver without any increase in the total fat as shown by analysis. We may, therefore, conclude that fatty degeneration represents either a fatty infiltration or an autolysis of cell proteins whereby bound lipins become visible upon being separated from their amino-acid linking.

V. ADIPOCERE.

The formation of adipocere was cited by Voit as evidence of the formation of fat from protein. There is an apparent replacement of the muscles of bodies buried in wet places by this wax-like material which is resistant to putrefaction. Van Itallie and Steenhauer⁵³ analyzed a sample of Fourcroy's adipocere which had been preserved for 130 years and found it to consist of a mixture of fatty acids, probably palmitic and stearic, with their calcium soaps. A small amount of cholesterol never before observed in adipocere was found.

Schmidt⁵⁴ found that in early Egyptian mummies 60 per cent. of the weight of the lungs and 30 per cent. of the spleen consisted of fatty acids and considered this conclusive evidence of the transformation of proteins into fat. Bernard reports the finding of the body of a drowned man encased in a coating of adipocere so light that it was floating in the sea after a long time. Wells^{42a} remarks about the extreme lightness of bodies which have undergone adipocere formation, some of them weighing as little as 20 pounds, which is no more than the weight of the adipose tissue alone of some bodies.

Wells^{42a} explains the process of adipocere formation as follows: The fatty acids of the fat tissue are neutralized by the ammonia formed during putrefaction which thereby removes these fatty acids from the normal balance of fat and fatty acids in the fat tissue; as a result the lipase of the fat tissue continues to split the fat, and more fatty acids are produced, which likewise go to form soaps. This continues until practically all the neutral fat has been decomposed, the glycerol diffusing rapidly away. The soluble soaps, which bacteria do not attack, diffuse into the softened muscle tissue, which they gradually replace in part. In the meantime, from the more soluble ammonium soaps, calcium and magnesium soaps are being slowly formed, according to the usual rule of double decomposition (that the least soluble salt will be formed under such conditions); or else, if an acid reaction develops, free fatty acids are precipitated. The oleic acid seems to be converted into the higher fatty acids. It is also possible that the saponification is due to the gradual action of the fluids produced in decomposition of the tissues, or to the alkalinity of the water in which the body lies. Possibly bacteria may be responsible for this decomposition of the fats rather than the body lipase, for Eijkmann⁵⁵ has observed that certain bacteria growing in fat-containing

agar produce calcium, ammonium and sodium soaps. Cevidalli⁵⁷, Ascarelli⁵⁸ and Schuetze⁵⁹, have made similar observations. There is, therefore, no evidence that fat is formed from protein in these cases.

VI. FORMATION OF FAT FROM PROTEIN BY LOWER FORMS OF LIFE.

Additional evidence cited to support the conversion of protein into fat is the supposed increase in fat in the ripening of cheese. Kondo⁶⁰ finds in the ripening of Cheddar cheese in the air that there is always a decrease in fat content. This begins in about ten days and increases with time depending upon the physical properties of the cheese and temperature. In one case he finds that nine per cent. of the fat content disappears after thirty days and twelve per cent. after forty days. Nierenstein⁶¹ confirms this fat decrease in the ripening of cheese.

Beebe and Buxton⁶² observed an abundant production of fat from proteins by the action of *Bacillus pyocyaneus* and fungi. Ritchie⁶³ observed the production of fat from glycerine-free agar by *Bacillus diptheriae* and *Bacillus anthracis*. Many observations on the increase in the fat content of mammalian organs undergoing autolysis may be due to failure to observe sterile conditions or to the use of micro-chemical methods for the detection of fat which does not show fatty acids in combination but only free fatty acids, and then the breaking up of the organs by autolysis or degeneration frees fatty acids which are detected by the method used although originally absent.

Neuberg and Rosenberg⁶⁴ found that from one kilogram of casein there was obtained by putrefaction 117 gm. of volatile fatty acids, forty-seven gm. of which was butyric acid. Since it is concluded that this acid originates from the deaminization of amino-butyric acid, the mother substance must be glutamic acid, which makes up ten per cent. of the casein molecule. The transformation of the glutamic acid takes place by splitting off carbon dioxide from one of its carboxyls and subsequent removal of the amino group, both of which reactions are well known to occur. Propionic acid could be formed in a similar way from aspartic acid. Similar results were obtained in the putrefaction of gelatine. This may be the explanation of the changes found in previous experiments under non-sterile conditions.

McClendon⁶⁵ finds that during the development of the *Cryptobranchus* egg there is an increase in the fatty acids of about eight per cent. During development of the brook trout egg this increase is about 5.6 per cent. In these eggs the vitellin is the chief reserve material and it seems probable that it is transformed into fatty substances.

Hoffman⁶⁶ took the eggs of *musca vomitoria* and divided the quantity in halves. One portion he analyzed for fats; the other portion he allowed to hatch out upon a blood of a low and known fat and sugar content. When the insects were grown he analyzed them, and found that they contained ten times as much fat as did the original eggs. This fat, he concluded, must have been from the proteins, and in the condition known as adipocere, large quantities of fat and fatty

acids are formed by bacterial action. This explanation, in all probability, holds for the experiments of Hoffman.

Another possible conversion of the protein into fat has been reported by Weinland^{5d}, who found that the larvae of the blow-fly (*Calliphora*) had the power to form fat from Witte's peptone in an atmosphere of nitrogen or hydrogen; i.e., in the absence of oxygen, by forming amino-acids. The larvae can deaminize the amino acids with the evolution of ammonia and then with the evolution of carbon dioxide can produce higher fatty acids which have been freed from amino groups. This is an additional explanation of the formation of fat from protein in many of the experiments which were conducted under conditions which would not exclude the blow-fly.

The evidence is convincing that there is not fat formation from proteins in the ripening of cheese, but that certain bacteria and other lower forms of life can form fat from protein.

VII. TRANSFORMATION OF FOOD FATS INTO TISSUE CARBOHYDRATES. HISTORICAL.

The formation of carbohydrate from fat in vegetable cells has been proven by Sachs⁶⁷, and many others, and is now an accepted fact. Couvreur⁶⁸ has demonstrated that the silk worm can effect a like transformation.

R. Du Bois⁶⁹ claims that the marmot can transform ordinary fats into carbohydrate during its winter sleep. This is disputed by Paul-esco⁷⁰ who thinks that the carbohydrate was derived from protein, but Du Bois says that the proteins were used in insufficient quantities to account for the change found.

Chauveau⁷¹ conducted experiments on the marmot and concluded that this animal can form carbohydrate from fat. Chauveau points out that the marmot when fasted in summer, dies after the loss of about 96 per cent. of its fats, and then has scarcely any carbohydrates left in the liver, muscles, or blood. After hibernation the marmot has used up its fat, but the blood still contains glucose and the liver and muscles contain glycogen. Chauveau considers this as evidence, after such a time of continued absence from food, with considerable expenditure in carrying on the vital activities of the body, that the carbohydrates (glycogen and glucose) had been formed from fat.

Seegen⁷² bled a dog to death and then removed the liver and minced it quickly. He divided the mixture into two parts, one of which he used as a control and to the other he added olive oil and incubated both at 35 to 40°C. At the end of five hours, he found an increase in reducing sugars as determined with Fehling's solution. He found an average increase of 47.5 per cent. which he interpreted as being formed from fat. This may have been due to the hydrolysis of the fats into fatty acids and glycerol by the lipases of the dead liver tissue, and the transformation of this glycerol into carbohydrate, since Cremer^{22c} has demonstrated the transformation of glycerol into carbohydrate in the dog. Woodyatt^{73a} has demonstrated that glyceric alde-

hyde and Ringer and Lusk⁷⁴ that glyceric acid can be transformed into carbohydrate.

Lusk (Science of Nutrition, p. 457), in connection with this transformation, states that giving fat along with meat to a diabetic will not increase the sugar in the urine, and he also cites experiments of his own on giving meat in diabetes which resulted in a decrease in the fat metabolism, as it would in the normal organism, yet there was no effect on the dextrose-nitrogen ratio; therefore the latter cannot be influenced by the *quantity* of the fat burned. Hartogh and Schumm⁷⁵ reported contrary results.

Falta, Eppinger and Rudinger⁷⁶ found a largely increased sugar output after administering adrenalin to depancreatized dogs. However, Ringer⁷⁷ found that the administration of adrenalin to a fasting phlorizinized dog at first did bring about an elimination of "extra sugar", which he claims was discharged from the glycogen repositories of the body on account of the anemia of the tissues, but a second injection of adrenalin was without influence on either the sugar or nitrogen elimination. This indicates that adrenalin does not cause a production of sugar from fat. Several cases of high dextrose-nitrogen ratios in human diabetes have been reported, but the highest is that obtained by Bernstein, Bolaffio, and Westenrijk⁷⁸. Their ratio, after allowing for the carbohydrates contained in the food, often reached D:N::10:1, instead of 3.65 to 1. The high ratios in diabetes are explained by Falta as being due to very great activity on the part of the adrenals, which not only inhibits the internal secretion of the pancreas, but also causes a production of sugar from fat. These high dextrose-nitrogen ratios, as well as many similar observations described in the literature are unquestionably due, in Lusk's opinion (p. 459) to the surreptitious ingestion of food containing carbohydrate.

In diabetes the organism loses the power to burn carbohydrates, and in extreme cases the ability to burn protein is also impaired and the respiratory quotient may sink very low. It has been claimed even that in diabetes the respiratory quotient may fall considerably below that of fat (.707), thus indicating that fat is being converted into carbohydrate, or some other relatively oxygen rich compound. More recent observations do not support this claim, and for the present we must assume that there is no direct evidence that fat is converted into carbohydrate in the phlorizinized or diabetic animal.

Woodyatt^{73b}, however, is not convinced and points out that fats of the diet in the course of digestion and intermediate metabolism must be saponified into glycerol and higher fatty acids before they can be oxidized. Fats such as tristearin, or an oil such as triolein, when completely saponified, yield approximately ten parts by weight of glycerol to 90 parts by weight of higher fatty acids. Since glycerol is capable of conversion into glucose in the body almost gram for gram, he says that for clinical purposes 100 gram mixed fat in the diet, if completely absorbed and catabolized, will introduce into the metabolism about 10 gm. of glucose and 90 gm. of fatty acid. He explains away the objections to this view, which may be based on the fact that in-

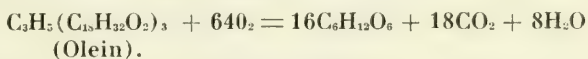
gested neutral fats have not been observed to cause the appearance of "extra glucose" in the urine of phlorizinized dogs, by suggesting that extra glucose should not be expected unless special precautions had been taken to discharge tissue fat, and further states that it is not improbable that the tissue fat catabolized by fasting phlorizinized dogs does produce glucose and that the glucose is then credited to protein.

Hari⁷⁹ found a respiratory quotient of 0.55 for hibernating rats, and Pembrey¹⁰ found that hibernating dormice gave respiratory quotients as low as 0.23, and hedge hogs, in their winter sleep, gave quotients of 0.50 and even 0.30 with a body temperature of 12°C.

In order better to understand these low respiratory quotients a general discussion of respiratory quotients will be first given. The carbohydrate molecule contains just sufficient oxygen to oxidize its own hydrogen. The carbon remaining requires one molecule of carbon dioxide. Therefore the ratio of the volume of the carbon dioxide given out to the volume of the oxygen consumed

$\frac{(\text{volume CO}_2 \text{ produced})}{(\text{volume O}_2 \text{ absorbed})}$ is 1:1. In a similar manner the respiratory quotient of pure protein is calculated from its empirical formula to be 0.801 and that of fat 0.707. (Lusk, Chapter II).

The oxidation of pure fat results in a lower respiratory quotient than the oxidation of either protein or carbohydrate. A respiratory quotient less than that of pure fat (0.707) means that an oxygen poor substance is being converted into an oxygen rich substance. The transformation of fat into a carbohydrate would give a respiratory quotient of 0.281^{10a} in accordance with the following equation:



$$\therefore \text{R. Q.} \frac{\text{CO}_2}{\text{O}_2} = \frac{18}{64} = 0.281$$

The low respiratory quotients of Hari and Pembrey mean an excessive absorption of oxygen or a markedly decreased excretion of carbon dioxide, or both. There is a marked decrease in both of the experiments of Pembrey because the body temperature of the marmot dropped to 12°C., and the total metabolism of the animal decreased until the carbon dioxide output was less than two per cent. as much as when the same animal was awake. This decrease was not so great in the oxygen, thus resulting in a marked drop in the respiratory quotient. Upon awaking the hedge hog's body temperature increased to 30°C., its total metabolism increased, and the respiratory quotient went up to 0.78, a value indicating the normal oxidation of two or even all three of the ordinary food stuffs. Pembrey interpreted his low results to mean that there was a conversion of fat into carbohydrate. This interpretation has been questioned but it seems certain that they represent incomplete oxidations and the formation of compounds richer in oxygen than is fat. The hypothesis that this oxygen rich compound is stored in the form of carbohydrate, thus representing a transformation of

fat into carbohydrate, is not entirely satisfactory because the total accumulation of oxygen stored in the tissues during the winter sleep would necessitate the accumulation of an amount of carbohydrate far in excess of the total carbohydrate content of the animals under any conditions. However, Robertson⁸⁰ points out that hibernating animals excrete in their urine notable quantities of products of incomplete oxidation, such as lactic acid; and it is probable that some of the excess of oxygen intake is disposed of in this way. It should also be noted that the complete transformation of fat into lactic acid and the excretion of this lactic acid would give the same respiratory quotient as the formation of glucose from fat. Glucose and lactic acid have the same empirical formula and it is immaterial whether the oxygen rich compound be stored or excreted since its effect on the respiratory quotient is the same in either case.

In the hedge hog experiments of Pembrey, the body temperature dropped from 30°C. to 12°C. and one would expect this to result in a change in the oxidation processes, which in this case is the partial oxidation of fat instead of its complete oxidation to carbon dioxide.

VIII. TRANSFORMATION OF PROTEIN INTO FATS.

If protein is converted into fat several conditions must be fulfilled: the respiratory quotient must be higher than that of protein itself; there must be a retention of protein carbon; a change in the chemical constituents of the blood would in all probability take place. These factors were studied with the methods described below.

I. EXPERIMENTAL METHODS.

First, the respiratory exchange and heat production of a dog stuffed with large quantities of lean beef heart were measured in a series of experiments. The respiration-calorimeter used belongs to the Department of Physiology, Cornell Medical College, and is under the direction of Dr. Graham Lusk. An abstract of these results has already been published by Atkinson and Lusk⁸¹; and another by Atkinson, Rapport and Lusk⁸² is in press. Second, an extensive study of the chemical changes taking place in the blood of dogs under similar conditions of meat stuffing was undertaken.

The principles and operation of the respiration-calorimeter are fully described by Lusk elsewhere^{43a}, and they will not be reviewed further.

Short haired female dogs having a quiet temperament are best for use in the respiration-calorimeter, since they can be kept clean and can be catheterized when it is desirable to collect the urine quantitatively. The animals must also be

capable of being trained to remain quiet in the respiration-calorimeter, so as not to increase the heat production by muscular movements.

All dogs were put on a standard diet sufficient to maintain their weight. This consisted of 100 gm. of lean beef heart, 100 gm. cracker crumbs, 10 gm. bone ash and 10 to 30 gm. of lard. Their minimal heat production and respiratory exchange was determined after the influence of the standard diet had ceased to affect their metabolism. This is found to be the case 14 hours after eating with the dog completely at rest, usually asleep. This level of metabolism is spoken of as their basal metabolism.

Considerable difficulty was found in persuading some dogs to take much meat especially on warm days. Bull dogs were found to be very good meat eaters.

The dogs were fed the quantity of lean beef heart, trimmed as free from fat as possible (given in column three, Table I) early in the morning and placed in the calorimeter at the time given in the last column of this same table. These hours were selected because they are the hours of maximum protein metabolism as shown by the quantity of nitrogen eliminated in the urine. (Table II, p. 36).

In the two investigations in which the chemical changes in the blood were studied, healthy and well nourished dogs were selected and placed on a liberal mixed diet. The dogs were fed late in the afternoon and a normal sample of blood drawn from the left heart through a hypodermic needle the next morning, at which time all the influence of digestion on the composition of the blood had ceased to operate. The sample of blood was too small to cause any changes due to hemorrhage. The dogs submitted without excitement in all cases. Immediately after drawing the first sample of blood, the dogs were fed the quantity of meat given in the tables which follow. A second sample of blood was drawn five to six hours after the dog had eaten all of the lean beef heart it could be persuaded to take. In some cases a third sample was taken twenty-four hours after the ingestion of the meat.

The method and apparatus described by Clark⁵⁴ were used to determine the hydrogen ion concentration which is expressed as the p_h . A saturated potassium chloride-calomel cell was made up every month and tested at frequent intervals against a buffer solution of potassium diacid phosphate and sodium hydroxide, with a p_h of 7.4. Several

TABLE I.
DATA — CALORIMETER EXPERIMENTS.

Experi- ment number	Date	Food	Number of hours	Effect of Meal Ingestion on Hourly Metabolism					Hours after food
				Urine Nitrogen	R. Q.	Calories		C deposited	R. Q. of deposited material
						Indirect	Direct		
27	1919 Feb. 6	Basal	2	grams 0.15	0.840	15.92	16.08	grams	(Weight 11.24 kg.)
30	Feb. 18	Meat, 800 gm.	3	1.46	0.800	31.47	32.75	0.66	4, 5, 6
31	Feb. 19	Meat, 900 gm.	3	1.47	0.787	34.33	34.14	0.48	4, 5, 6
32	Feb. 20	Meat, 1000 gm.	4	1.46	0.808	34.90	35.87	0.32	4, 5, 6, 7
33	Feb. 21	Meat, 1100 gm.	2a	1.45	0.831	31.65	31.36	0.56	4, 5
34	Feb. 24	Meat, 1080 gm. *	2b 2	1.45 1.57	0.843 0.800	35.28 34.00	34.54 34.12	0.25 0.70	6, 7 4, 5
35	Feb. 26	Basal	3	0.27	0.820	19.74	19.59	—	(Weight 12.07 kg.)
36	Feb. 27	Basal	3	0.20	0.830	18.25	17.16	—	—
37	Feb. 28	Basal	2	0.17	0.850	17.30	16.95	—	—
38	Mar. 1	Basal	2	0.15	0.820	18.21	(18.21)	—	—
39	Mar. 3	Basal	3	0.15	0.850	17.57	17.22	—	—
43	Mar. 12	Basal	2	0.15	0.810	17.08	16.99	—	(Weight 11.50 kg.)
46	Mar. 17	Meat, 1200 gm.	3	1.02	0.796	26.57	28.10	—	5, 6, 7 **
47	Mar. 18	Meat, 800 gm.	3	1.44	0.795	29.90	30.77	0.77	5, 6, 7
48	Mar. 19	Meat, 800 gm.	4	1.35	0.793	29.37	30.27	0.61	5 to 8
49	Mar. 22	Basal	2	0.23	0.790	17.72	17.54	—	—
50	Mar. 24	Basal	2	0.16	0.840	17.26	16.87	—	—
51	Mar. 28	Meat, 800 gm.	4	1.02	0.795	27.04	27.52	—	5 to 8 ***
54	Apr. 15	Meat, 800 gm.	4	1.41	0.794	31.07	30.57	0.59	5 to 8
55	Apr. 16	Meat, 1000 gm.	4	1.58	0.797	31.97	31.98	0.91	5 to 8
56	Apr. 19	Meat, 1300 gm.	4	1.47	0.826	31.62	33.25	0.59	5 to 8 **
						508.22	571.85		

* Standard diet at 5 p.m. and thereafter daily until March 15.

** After a fast of one day.

*** After a fast of four days.

experiments were made in the beginning of the investigation of the relative value of the Clark and McCleendon⁸⁴ electrodes. The results obtained showed a variation in p_h of the same samples of blood of 0.05, if the readings were taken within 10 or 15 minutes from the time of the drawing of the blood. These findings, and the fact that the McCleendon vessel is more difficult to manipulate, determined the use of the Clark vessel. It was found that the whole blood and the plasma, obtained by centrifuging the oxalated blood in a closed tube, gave correspondingly parallel changes; therefore, the plasma was used, since the hydrogen vessels could be kept clean more easily with it and there was no danger of the oxygen of the red cells uniting with the hydrogen on the platinum, thus reducing its concentration.

The carbon dioxide-combining capacity of the blood plasma was determined by the method of Van Slyke^{85a}; the urea nitrogen by the method of Van Slyke and Cullen⁸⁶; total fats^{87a}, cholesterol^{87b} and lecithin^{87c}, according to Bloor with a slight modification in the method for total fat. It was found more convenient and more accurate to saponify, in a Florence flask, both the standard oleic acid and the fat in the sample of blood and to dissolve the resultant mixture in five cubic centimeters of ether-alcohol solution. The water was added to this solution, thus avoiding the transfer of the solution with a possible loss. This resulted also in the addition of the same amount of color to both the standard and the sample, since a slight brownish color always develops in the stock solution of sodium ethylate used in the saponification. The non-protein nitrogen^{88a}, the creatinine^{88a} and the blood sugar^{88b} were determined by the methods of Folin and Wu. The oxygen capacity of the whole blood was determined according to the method of Van Slyke^{85b}. A Kober nephelometer-colorimeter was used throughout.

TABLE II.
Urinary Nitrogen.

In order to determine the hour of maximum protein metabolism, Dog 14 was fed 800 gm. of meat, catheterized hourly and the total nitrogen in the urine determined by the Kjeldahl method. The following results were obtained:

Hour	Grams Nitrogen
Fourth	1.29
Fifth	1.51
Sixth	1.56
Seventh	1.57
Eighth	1.49
Ninth	1.49
Tenth	1.41

The nitrogen eliminated hourly in the urine is the basis for the calculation of the amount of protein destroyed in the

body. From this it is possible to calculate the amount of oxygen required for its destruction, the amount of carbon dioxide which would be eliminated if the reaction were complete, and also the heat which would be produced thereby. The quantity of fat retained could be estimated from the difference between the quantity of respiratory carbon obtainable from the protein metabolized and the quantity actually eliminated in the respiration. The calorific value of this deposited fat can then be calculated directly.

Experiment 55, Table I, will illustrate the method of calculation used.

Nitrogen in urine = 1.58 grams per hour.

N—CO ₂	gm. 14.77	N—O ₂	gm. 13.33	Nitrogen	cal. 41.89
Resp. CO ₂	11.42	Resp. O ₂	10.42	Dep.	9.92
Dif.	3.35		2.93	Indirect	31.97
				Direct	31.98
R. Q. per hour 0.81, 0.74, 0.80, 0.84					
R. Q. for whole period 0.797					

N—CO₂ is the amount of carbon dioxide derivable from the protein metabolized in one hour.

N—O₂ is the amount of oxygen necessary to oxidize the protein metabolized in one hour.

Resp. CO₂ and Resp. O₂ are the amounts of carbon dioxide and oxygen which were actually respired during an hour.

The difference represents (1) the carbon dioxide which would have been expired had all the retained carbon of the part metabolized been oxidized and (2) the oxygen which would have been employed in that process. The relation between the volumes of these two gases indicated that the material retained and unoxidized would have yielded a respiratory quotient of 0.83, which indicates the retention of a portion approximately half of the calories of which were derived from fat and half from glucose.

N—calories is the quantity of heat which would have been eliminated by the dog had all the protein metabolized by the dog been completely oxidized. From this is subtracted the number of calories estimated to have been retained as a mixture of fat and glucose, as stated above. The difference represents the calories, as calculated by indirect calorimetry,

which in this case agrees exactly with those directly measured by the method of direct calorimetry.

In another experiment⁸² the following values were obtained for the fifth hour:

	CO ₂ gm.	O ₂ gm.	Calories
Equivalent of 1.44 gm. urinary N	13.46	12.17	38.17
Found in respiration.....	10.10	8.72	11.32
	3.36	3.45	26.85

R. Q. of deposit = 0.708

Value of fat deposited = 11.32 calories

Calories (indirect) = 26.85

Calories (direct) = 27.52.

C retained = 0.92 gm. { = 1.2 gm. fat

{ = 2.3 gm. glucose (8.63 calories)

Calories if C had been retained as glycogen = 29.54.

During the period of experimentation twelve alcohol checks were made. The average of all the respiratory quotients was 0.668 (theory 0.667) and the heat recovered was 0.3 per cent. greater than the heat calculated as obtainable from the combustion of the alcohol.

III. DISCUSSION OF CALORIMETER EXPERIMENTS.

It will be remembered that when the protein of meat is oxidized in the body the respiratory quotient is 0.801.

It is evident from the table that in ten experiments, after giving meat amounting to between 700 and 1300 gm. daily, the respiratory quotients varied between 0.787 and 0.808, as appears below.

Experiment Number	48	54	51	47	46	55	30	34	32
R. Q.	0.793	0.794	0.795	0.795	0.796	0.797	0.800	0.800	0.800
R. Q. of deposit	0.860	0.860		0.840		0.830	0.830	0.830	0.770

In experiments 51 and 46 there was no retention of protein carbon, whereas in six of the experiments the retained carbon was held in such a form that, had it been oxidized, it would have yielded respiratory quotients of between 0.83 and

0.86, which indicate the retention of a pabulum containing only about half of its calories in fat and half in carbohydrate. By weight this would indicate the retention of approximately one gram of fat to every two grams of glycogen. The calculation showing this is given on page 585.

As the respiratory quotient of fat is 0.707, the above results warranted the conclusion that in the case of excessive ingestion of meat by a dog the retained pabulum might be laid down as fat when the circumstances were favorable. It was noted that it was very difficult to induce the dog to take meat in these very large quantities.

It can be seen on page 585 that, computed on the basis of the oxygen absorption by the method of indirect calorimetry, the calculated heat production agrees more closely with the value obtained when the computation is based upon the hypothesis that the carbon retained is laid down in the form of fat. A quite different value is obtained if the calculation is based on the assumption that the carbon is laid down as glycogen. Based on the first hypothesis, the heat production calculated by the method of indirect calorimetry fails to agree with that directly measured by only 2.3 per cent; based on the second hypothesis the failure to agree is 7.4 per cent.

It is impossible to secure beef heart entirely free from fat and the beef heart used contained approximately one per cent of fat. However, this small quantity of fat if deposited in the body would have no effect on either the heat production or respiratory exchange, since under this assumption it would undergo no chemical change requiring the consumption of oxygen. If burned, it would lower the respiratory quotient, since fat has a respiratory quotient of 0.707. The conclusions of this experiment are based on a rising non-protein respiratory quotient, therefore, the method of calculating the calories by indirect calorimetry is still correct and is even more accurate than the figures show. A few experiments in which fat was added to the beef heart are reported elsewhere. (Table VI).

Now in reference to possible objection on account of the presence of glycogen in the beef heart fed, Schöndorff⁹¹ fed dogs much carbohydrate and analyzed their tissues for glycogen. He found as low as 0.10 per cent. in heart muscle even under these conditions, which is higher than would be

present in the hearts used, since these animals are not fed previous to slaughter.

It should be remembered that almost a tenth of the meat fed, under maximum conditions, was changed into fat; therefore, the small traces of fat and glycogen which might be present are not sufficient to invalidate the conclusions.

It must be remembered, however, that the conditions were exceptional in that the animal weighing only 11.4 kilograms consumed on some days ten per cent. of its own weight of lean beef heart and that while on this high nutritive plane the glycogen reservoirs would be filled. Under these circumstances fragments of protein metabolism which would ordinarily have been oxidized or converted into glucose and laid down as glycogen, found no other pathway open than conversion into fat. Under a normal mixed diet these conditions would not exist.

IV. DATA — CHEMICAL ANALYSES OF BLOOD.

The effect of a mixed diet on the chemical changes of the blood were first studied for comparison, and these results are presented in Table III, p. 588. During this series of experiments the dog was fed the mixed diet described on page 581. The changes of the blood of several different dogs under heavy meat stuffing were then studied. These results are given in Tables IV, p. 589; V, p. 590.

To rule out the effect of slight traces of fat still in the beef heart, I added thirty grams of lard to the usual meat diet and determined the blood fat (Table VI, p. 590) during the fifth hour, which is the period of maximum protein and fat metabolism when both are given in large quantities, but later than the period of fat metabolism when fat is given in small quantities mixed with large quantities of protein.

TABLE III.

The effect of a mixed diet upon the chemical composition of the blood.

Dog No.	Experiment No.	Date	Sugar		Fat		CO ₂		Non-protein Nitrogen per 100 cc.	
			A	B	A	B	A	B	A	B
		1921	per cent	per cent	per cent	per cent	vol. per cent	vol. per cent	mg.	mg.
I	1	July 7	0.098	0.109	0.79	0.77	40.0	41.0	24.0	27.0
I	2	" 8	0.104	0.113	0.78	0.76	40.0	50.0	22.0	26.0
I	3	" 21	0.103	0.112	0.77	0.76	45.0	46.8	23.0	26.0
I	4	" 22	0.096	0.106	0.78	0.77	43.5	54.0	28.0	30.0
I	5	" 27	0.109	0.107	0.76	0.74	42.5	50.0	26.0	28.0
II	1a	" 7	0.101	0.129	0.89	0.87	42.0	41.0	25.0	27.0
II	2a	" 8	0.103	0.111	0.87	0.84	40.3	46.1	28.0	29.0
II	3a	" 21	0.098	0.115	0.85	0.82	43.7	49.1	24.0	27.0
II	4a	" 22	0.102	0.110	0.87	0.79	48.0	52.0	26.0	30.0
II	5a	" 27	0.106	0.122	0.85	0.85	49.0	59.0	23.0	29.0
Averages			0.102	0.113	0.82	0.80	42.7	48.9	25.0	28.2
Change, per cent				+10.8		-2.5		+11.9		+12.8

Column A contains the readings taken twenty-four hours after the partaking of food; Column B, five hours after partaking of the mixed diet which was fed immediately after drawing sample A.

TABLE IV.

Effect of stuffing the dog with large quantities of lean beef heart on the chemical composition of the blood.

Dog No.	Experi- ment No.	Date	CO ₂		Sugar		Total Fat		Cholesterol		Non-protein nitrogen per 100 c. c.		Meal fed.
			A	B	A	B	A	B	A	B	A	B	
		1921	vol. per cent	vol. per cent	per cent	per cent	per cent	per cent	per cent	per cent	mg.	mg.	gms.
IV	1	Dec. 15	48.0	51.0	0.096	0.184	0.83	1.02	0.133	0.133	32.2	56.0	1400
IV	2	Dec. 16	45.6	50.0	0.162	0.167	0.99	1.12	0.208	0.192	29.4	67.2	1500
IV	3	Dec. 17	42.4	47.5	0.150	0.171	0.89	1.00	0.178	0.204	33.6	57.5	950
IV	4	Dec. 18	38.0	45.5	0.120	0.171	0.83	0.97	0.178	0.192	29.4	60.2	1300
IV	5	Dec. 19	46.2	51.0	0.139	0.166	0.97	1.04	0.128	0.232	29.4	50.4	1200
IV	6	Dec. 20	44.0	45.0	0.156	0.170	1.12	1.18	0.132	0.147	36.6	65.8	1750
		1922											
XIV	7	Apr. 14	52.0	62.1	0.091	0.097	1.38	1.11	0.136	0.136	23.8	43.4	1500
XIV	8	Apr. 17	51.2	55.0	0.103	0.113	1.33	1.29	0.126	0.114	21.0	44.8	1500
XIV	9	Apr. 18	53.0	60.0	0.103	0.122	1.29	1.43	0.116	0.148	21.0	49.2	1500
XIV	10	Apr. 19	59.8	61.0	0.117	0.117	1.28	1.34	0.156	0.149	28.0	45.5	1200
XIV	11	Apr. 20	58.8	61.0	0.117	0.122	1.27	1.34	0.119	0.135	21.0	49.1	1350
XIV	12	Apr. 21	54.0	56.0	0.125	0.128	1.29	1.35	0.156	0.215	22.2	44.8	1000

Column A contains the readings for a normal dog twenty-four hours after eating and just before stuffing with meat; Column B, six hours after A.

TABLE V.

Effect of stuffing the dog with large quantities of lean beef heart on the chemical composition of the blood.

Dog No.	Experiment No.	Date	Sugar		Fat		CO ₂		Non-protein nitrogen per 100 cc.		Meat Fed.
			A	B	A	B	A	B	A	B	
		1921	per cent	per cent	per cent	per cent	vol. per cent	vol. per cent	mg.	mg.	gms.
I	6	July 28	0.101	0.126	0.78	0.84	46.0	54.0	23.0	60.0	1300
I	7	" 29	0.098	0.095	0.78	0.86	43.0	49.8	27.0	53.0	800
I	8	Aug 4	0.102	0.108	0.77	0.80	45.0	51.2	28.0	52.0	1200
I	9	" 10	0.130	0.085	0.73	0.76	55.0	60.0	29.0	59.0	1500
II	6a	July 28	0.104	0.100	0.77	0.84	42.1	50.0	29.0	62.0	2100
II	7a	" 29	0.101	0.105	0.78	0.86	34.0	42.0	34.0	56.0	800
II	8a	Aug 4	0.098	0.101	0.79	0.85	44.5	51.0	30.0	55.0	1600
II	9a	" 10	0.134	0.104	0.77	0.79	48.0	58.1	41.0	56.0	1900
II	10a	" 11	0.101	0.097	0.79	0.85	46.5	53.0	35.0	61.0	800
Averages Change, per cent			0.101	0.109 +7.9	0.76	0.83 +9.2	44.8	52.1 +16.3	30.6	57.1 +80.5	

Column A contains the readings taken just before eating; Column B, five hours after feeding.

TABLE VI.

Effect of the addition of 30 gm. of lard to a diet of 800 gm. of lean beef heart on the blood fat.

Dog No.	Date	Fat	
		A	B
	1921	Per cent.	Per cent.
I	August 23	0.82	0.81
I	" 23	0.87	0.81
II	" 23	0.88	0.85

Column A contains the readings taken for a normal dog just before eating; Column B, six hours after A.

In Table III, p. 588, it is seen that the average change in blood sugar in ten experiments, five hours after feeding a mixed diet, is a relative increase of 10.8 per cent.; at the same time the total blood fat decreased 2.5 per cent.; the carbon dioxide combining power of the blood plasma increased 11.9 per cent. and the non-protein nitrogen increased 12.8 per cent.

The results of the meat stuffing experiments in Table IV, p. 589, have not been averaged because the conditions of the dogs at the start were not quite the same and the condition of each dog varied from day to day as the glycogen reservoirs became filled. Dog IV was fed a mixed diet daily before Experiment One, and thereafter she was fed meat on consecutive days as shown in Table IV. Therefore, the glycogen reservoirs were comparatively well filled at the start. Dog XIV was fasted for four days before Experiment Seven, and three fast days elapsed between Experiments Seven and Eight. Experiments Nine to Twelve were on consecutive days. The glycogen reservoirs were, therefore, depleted on the days of Experiments Seven and Eight.

It is evident, however, that there is an increase in the carbon dioxide combining power of the blood plasma of about the same magnitude as that found under the influence of a mixed diet. Dog IV shows more marked changes in blood sugar under the influence of heavy meat stuffing than dog XIV. Dog IV had a normal blood sugar of 0.096 at the beginning of the experiment and this rose to 0.184, or a relative increase of 91.7 per cent. six hours after ingesting 1400 gm. of lean meat. The blood sugar of this dog remained high throughout the six days until it had increased to 0.156 per cent. on the morning of the sixth day. This further increased to 0.170 per cent. after the ingestion of 1750 gm. of meat, or a relative increase of 62.5 per cent. from sample A on the first day. The relative increase in blood sugar on the sixth day (Experiment Six, Table IV) was only 8.9 per cent., but this increase was 77.1 per cent. when compared with the first sample of this series.

The results on the blood sugar of dog XIV under the same condition are not so marked but are, nevertheless, decisive. Sample B, Experiment Twelve, after five days of continuous protein stuffing, shows an increase of 40.6 per cent. in blood sugar as compared with the first sample of the series.

In dog IV, on continuous protein stuffing, the relative in-

crease in six hours in the blood fat on the first day was 22.9 per cent. This continued to increase and to remain at a higher level until it reached 34.9 per cent. above the first sample on the morning of the sixth day. This high level was further increased only five per cent. upon ingesting 1750 gm. of meat on this day. (Experiment Six).

A somewhat similar condition exists in the case of dog XIV, except on the first two days (Experiments Seven and Eight) previous to which the dog was fasted as pointed out above. When protein stuffing is preceded by fast days there is a drop in the blood fat. This was also the case on April 17, but the drop is not so great. Beginning April 18, the second day of continuous protein stuffing, there is a relative increase in the blood fat of 10.9 per cent. when 1500 gm. of meat was ingested. On succeeding days the dog would not eat so much meat and the increase was not so great.

The results on cholesterol, while not of particular significance, are included. The non-protein nitrogen of the blood was approximately doubled.

Additional results are given in Table V, p. 590. In these experiments the meat stuffing was not continuous. There were intervening periods of feeding on a moderate mixed diet. These results while not so striking are in the same general direction.

One dog, not included in the tables, was pregnant during the series, and as she approached term she gave a greater increase of blood fat five hours after meat stuffing.

Table VI, p. 590 shows that the addition of 30 gm. of lard to 800 gm. of lean meat did not increase the blood fat six hours after its ingestion.

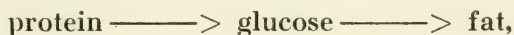
V. DISCUSSION OF CHANGES IN THE BLOOD UNDER THE INFLUENCE OF MEAT STUFFING.

That there is a slight increase in the alkali reserve as shown by the increase of the carbon dioxide combining power of the blood plasma when dogs are on a mixed diet, corresponds to the "alkaline tide" in the blood and urine following meals. That there is also an increase in the "alkaline tide" after stuffing with lean meat answers the possible objection that changes in the blood sugar and blood fat might be due to a depletion of the alkali reserve of the blood. The increase in the blood

sugar after meat stuffing is from two to six times greater than after feeding a mixed diet containing 100 gm. of cracker crumbs. This indicates a production of blood sugar from protein. The greater relative increase in the blood sugar five hours after feeding during the first days as compared with later days is due to the fact that the body cells have a plethora of glucose and glycogen molecules and then the excess goes to form fat, probably in accordance with the scheme shown on the next page. During the feeding of a mixed diet there was no increase in blood fat, but the considerable increase on the days of heavy meat stuffing indicated the formation of fat from protein. The increase in non-protein nitrogen in the blood gives some index of the intensity of the protein metabolism under these conditions. A general summary is given later.

VI. CHEMICAL PATHWAY OF THE TRANSFORMATION OF PROTEIN TO FAT.

Because meat under certain conditions may yield 58 per cent. of glucose in its metabolism (p. 567) and sugar in excess may be converted into body fat (p. 568), one is apt to assume (p. 568) that fat formation from protein is a common occurrence. That is to say the pathway of the transformation is



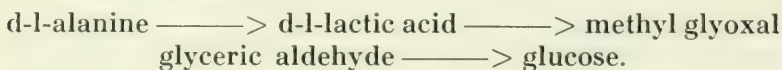
or as represented graphically on page 597, ABC, in which case the glucose is an intermediary product in this transformation. However, the conditions for glucose formation from protein are quite different from those for fat formation from protein, which do not directly involve the intermediary production of glucose. It is only during the ingestion of relatively small amounts of protein that glucose is formed from the deaminized residues of some of the amino acids derived from the metabolism of the ingested protein. When larger amounts of protein are ingested the glycogen depots of the body become saturated with deposited glycogen, and then this pathway becomes closed and fat is formed from the excess protein. This transformation behaves much the same as the continuation of a reversible reaction which will continue, in a given direction, until prevented by the accumulation of the products of that

reaction. This excess protein may cause the reaction to go to completion in some other direction, in this case fat formation. Therefore, the chemical pathway of the formation of fat from protein is only in part the same as the transformation of protein to glucose and glucose to fat. That is, the usual intermediary reaction in the formation of carbohydrate from amino-acids proceeds to a stage which is common to both carbohydrate formation from amino-acids and fat formation from carbohydrate, and then the completion of the reaction of protein to carbohydrate may be prevented by a plethora of glycogen molecules already formed and the reaction goes off into another direction, in this case fat formation directly from protein. (A, D, C, p. 597).

It is unnecessary to assume that glucose is continually formed. This would be the indirect path. The path I have indicated is the more direct one. The intermediary metabolism of these transformations will help to make this point clear.

It is well known that proteins are split into amino acids in the body, and of these acids glycocol, d-alanine, l-serine, cystine, proline, arginine, aspartic and glutamic acids, can form glucose^{43b}. The intermediary transformation of alanine will be discussed as a type.

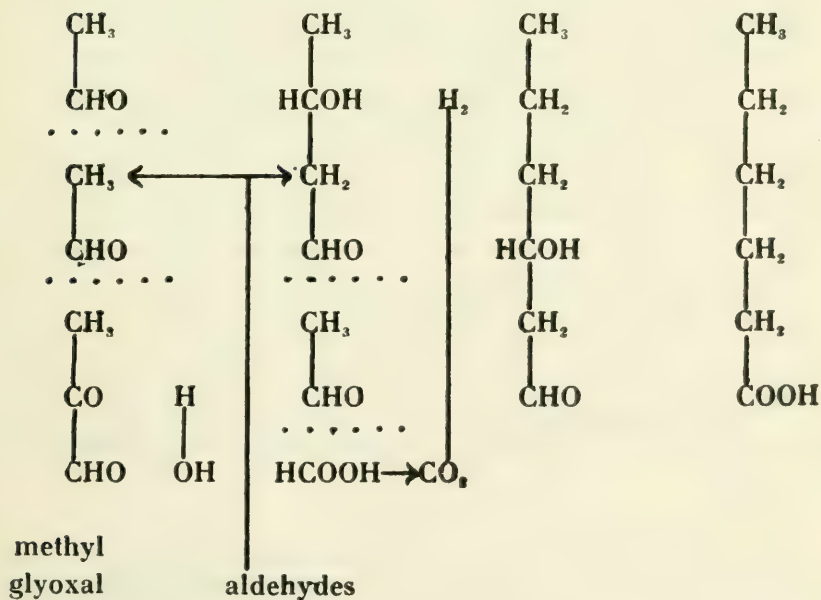
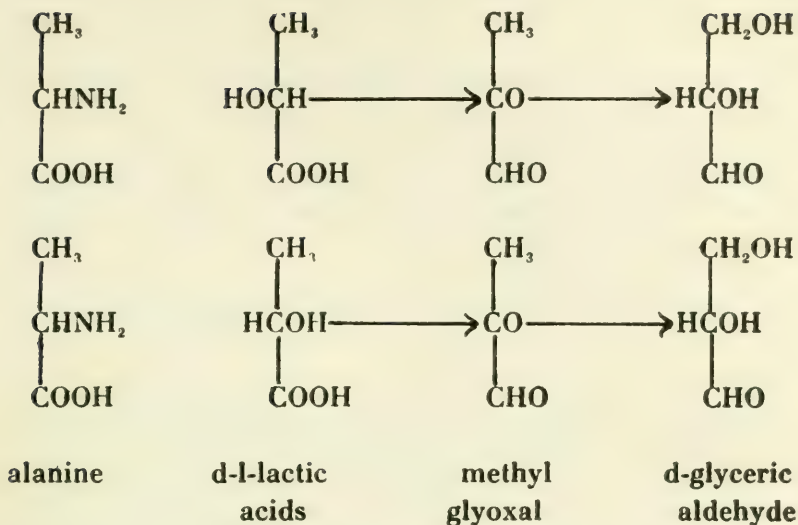
Experiments by Dakin⁸⁹ and by Neuberg⁹⁰ have led them to visualize the transformation of protein into glucose through the following stages:



The mechanism of this is discussed in detail by Lusk⁴³, pp. 192 and 268. Magnus Levy suggests that the transformation of carbohydrate into fat is probably due to the formation of aldehydes and methyl glyoxal and their condensation into higher aldehydes.

It should also be remembered that if an inadequate supply of oxygen be present in the tissues, lactic acid will be formed from glucose. For the above reasons lactic acid, methyl glyoxal and glyceric aldehyde may be intermediate products in both the transformations:

(a) protein \longrightarrow glucose (b) glucose \longrightarrow fat,
and it is through these products that the transformation
protein \longrightarrow fat proceeds since the pathway



protein ———— > glucose ———— > fat is closed on account of the saturation of the body cells with glycogen and this reaction takes a shorter path which may be pictured as shown on page 595.

As soon as the aldehyde radical at the end of the chain becomes oxidized the fatty acid is completed and the process of addition is terminated.

A graphic representation of these transformations is presented on the following page: the shorter path referred to above being A D C, and not A B C.

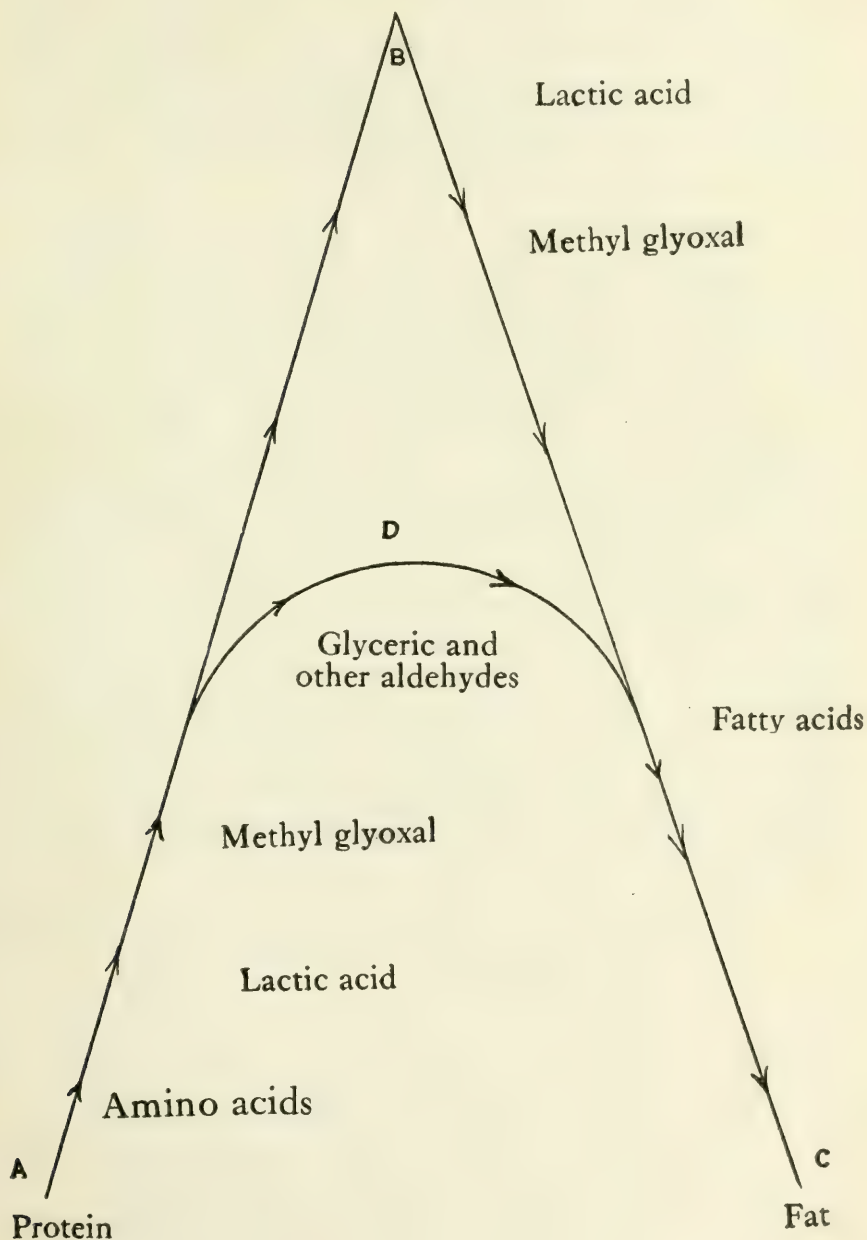
IX. TRANSFORMATION OF FOOD FATS INTO TISSUE CARBOHYDRATES — EXPERIMENTAL.

It has been pointed out (p. 580) that one might expect the reduction in oxidative processes of the hibernating hedge hog and marmot to favor the production of sugar from fat. The evidence that hibernating animals can form sugar from fat seems convincing. The respiratory exchange, respiratory quotients and body temperature of hibernating animals are much below normal (p. 579). This must decrease oxidative processes. The oxidative processes of animals under the influence of morphine are also greatly reduced, as will be shown later. In this connection the findings of Higgins and Means⁹² are very significant. They found a fall from 0.75 to 0.70 in the respiratory quotients of a man under the influence of morphine. These low respiratory quotients have been explained as being due to a change in the character of the metabolism, such as incomplete combustion, resulting in formation of acetone bodies from fat, or to the changing of fat to sugar. Therefore, experiments were undertaken to study the changes taking place in blood under the influence of morphine alone, during the ingestion of large quantities of fat alone, and during the ingestion of large quantities of fat while under the influence of morphine.

1. METHODS.

The methods of analysis of blood already described were used in this series. A normal sample of blood was drawn and then one grain of morphine sulphate injected subcutaneously in divided doses. Other samples were drawn at the intervals stated in Tables VII, VIII, and IX. Olive oil was the fat used

*Graphic Representation of the Transformation of
Protein into Fat.*



and it was given through a stomach tube. It was found that this oil in quantities of 100 c.c. and over is very apt to cause vomiting and diarrhea in dogs. It was found that at least a week of liberal feeding had to intervene before dogs would tolerate a second dose, and some dogs do not tolerate even smaller quantities and could not be used. For this reason, only a few dogs were available for this series and only smaller quantities of oil could be given to those not receiving morphine.

2. DATA — MORPHINE AND FAT STUFFING EXPERIMENTS.

The reduction in the oxidation processes under the influence of morphine was investigated and these results are presented in Table VII, p. 599. The next phase investigated was the effect on the chemical composition of the blood when fat was given to a dog under the influence of morphine. These results are presented in Table VIII, p. 600. The third phase of the investigation was the changes in the blood under the influence of fat stuffing alone. These results are given in Table IX, p. 601.

Upon inspecting Table VII, it is seen that the carbon dioxide combining capacity of the blood plasma is increased from a normal value of 50 to 56 volume per cent., or a relative increase of 12 per cent. two and one-half hours after the subcutaneous injection of morphine and that this had further increased to 16 per cent. above normal seven hours after the injection of morphine, but had returned to normal in 24 hours.

The oxygen capacity of the blood increased from 25.5 to 26.8 volume per cent., or a relative increase of five per cent. in two and one-half hours, and it had dropped five per cent. below normal at the end of seven hours.

TABLE VII.

Effect of the subcutaneous injection of one grain of morphine sulphate on the chemical composition of the blood of the dog.

Dog No.	Experiment No.	Date	CO ₂			O ₂			Sugar			Fat.			Cholesterol			Lecithin		
			A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
		1921-2	vol. per cent	vol. per cent	vol. per cent	vol. per cent	vol. per cent	vol. per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent
IV	1	Dec. 7	43	58	46	28.3	27.2	25.3	0.093	—	—	0.83	0.86	—	0.178	0.159	—	0.20	0.21	—
IV	2	Dec. 8	46	56	—	28.0	40.3	—	0.100	—	—	0.74	0.83	—	0.173	0.231	—	0.27	0.27	—
VI	3	Dec. 9	44	46	—	26.3	—	—	—	—	—	0.93	—	—	0.169	—	—	0.24	—	—
VI	4	Dec. 12	52	64	64	22.2	22.2	19.8	0.086	0.097	0.097	0.73	0.87	0.91	0.112	0.130	0.104	0.30	0.18	0.34
VIII	5	Dec. 15	54	54	—	20.3	—	—	0.068	0.120	—	0.85	0.95	—	0.125	0.139	—	0.47	0.45	—
VIII	6	Dec. 16	54	54	—	27.3	—	—	0.100	0.108	—	0.93	0.91	—	0.147	0.164	—	0.41	0.36	—
VIII	7	Dec. 19	42	53	60	18.3	21.4	18.3	0.107	0.150	0.130	1.00	1.16	1.02	0.166	0.200	0.166	0.26	0.15	0.16
VIII	8	Dec. 20	53	63	60	16.8	27.3	27.3	0.098	0.125	0.103	0.89	0.93	1.10	0.156	0.104	0.187	0.50	0.39	0.41
VIII	9	Dec. 21	53	61	58	19.3	—	20.8	—	0.187	—	0.78	0.85	0.80	0.093	0.096	0.093	0.26	0.26	0.24
IX	10	Jan. 9	58	60	60	31.7	30.3	33.3	0.077	0.140	0.120	0.91	0.97	1.05	0.140	0.150	0.120	—	—	—
IX	11	Jan. 11	55	55	—	30.8	34.8	—	0.072	0.118	—	1.00	1.00	—	0.170	0.160	—	—	—	—
IX	12	Jan. 13	55	—	—	30.4	33.4	—	0.105	0.200	—	0.94	0.93	—	0.167	0.131	—	—	—	—
IX	13	Jan. 16	47	50	—	30.4	30.2	—	0.970	0.143	—	0.95	1.05	—	—	—	—	—	—	—
Averages			50	56	58	25.5	26.8	24.1	0.091	0.139	0.112	0.88	0.94	0.98	0.15	0.15	0.13	0.32	0.29	0.29
Change, per cent				+12.0	+16.0		+5.0	+5.0		+53.0	+23.0		+6.0	+10.0			-13.0		-9.0	-9.0

Column A contains the reading taken for a normal dog just before injecting morphine; Column B, two and one-half hours after injecting morphine; Column C, seven hour after injecting morphine.

TABLE VIII.

Effect of the ingestion of large quantities of fat on the chemical composition of the blood of dogs after the subcutaneous injection of one grain of morphine sulphate.

Dog No.	Experiment No.	Date	CO ₂			Sugar			Total Fat			Cholesterol			No-protein nitrogen per 100 cc.			Fat given cc.
			A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	
		1922	vol. per cent	vol. per cent	vol. per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	mg.	mg.	mg.	
XI	1	Mar 29	39	44	42	0.093	0.127	0.095	0.93	1.01	1.49	0.142	0.119	0.136	30.8	23.8	33.6	200
XII	2	Mar 30	49	43		0.092	0.222	0.154	0.95	1.03	1.51	0.164	0.170	0.173	35.0	33.6	33.6	200
XII	3	Apr 3	42	53	51	0.091	0.126	0.090	0.94	1.00	1.43	0.184	0.208	0.215	35.0	23.8	32.2	200
XIII	4	Apr 5	42	42	42	0.093	0.192	0.166	0.91	0.99	1.65	0.108	0.178	0.119	37.8	29.4	32.2	300
XVI	17	Apr 24	54	51	58	0.084	0.182	0.117	0.93	1.03	1.51	0.172	0.111	0.156	25.2	25.2	33.6	125
XIV	18	May 1	51	46	46	0.091	0.103	0.130	0.95	1.04	1.62	0.116	0.179	0.179	23.8	25.6	26.4	150
XVII	19	May 1	50	51	53	0.094	0.146	0.136	0.89	1.05	1.50	0.116	0.204	0.223	26.6	21.2	19.2	150
Average,			46.8	47.1	45.3	0.091	0.157	0.127	0.93	1.02	1.53	0.143	0.167	0.172	30.6	26.1	29.5	
Change, per cent				+0.6	-3.0		+72.0	+39.0		+10.0	+64.0		+16.0	+19.0		-14.7	-3.49	

Column A contains the readings taken just before the injection of morphine; Column B, one and one-half hours after the injection of morphine, and just before giving olive oil through a stomach tube; Column C, six hours after B.

TABLE IX.

Effect of the ingestion of large quantities of fat on the chemical composition of the blood.

Dog No.	Experiment No.	Date	CO ₂		Sugar		Total Fat		Non-protein nitrogen per 100 cc		PH		Fat given
			A	B	A	B	A	B	A	B	A	B	
		1921	vol. per cent	vol. per cent	per cent	per cent	per cent	per cent	mg.	mg.			grams
XIV	5	April 6	45	52	0.090	0.118	0.93	1.35	30.8	21.0	7.39	7.11	200
XIV	6	April 10	52	52	0.089	0.092	0.95	1.33	28.0	16.8	7.47	7.34	200
XIV	7	April 12	52	38	0.096	0.130	0.97	1.37	29.2	21.0	—	—	150
XVI	8	April 13	53	—	0.102	0.122	0.95	1.43	29.8	29.2	7.40	7.34	150
XVII	20	May 10	49	42	0.089	0.089	1.05	2.00	—	—	7.41	7.38	100
XIV	21	May 10	48	44	0.091	0.091	1.02	1.60	—	—	7.47	7.25	100
Averages 50.0			46.6	46.6	0.093	0.107	0.98	1.51	29.5	22.0	7.43	7.26	
Change, per cent			—8.8	—8.8		14.0		53.0		—25.4		—23.0	

Column A contains the readings taken in the morning just before giving the olive oil; Column B, six hours after A.

The normal blood sugar was found to be 0.09 per cent. and this was increased to 0.14 per cent. in two and one-half hours, or a relative increase of 53 per cent. This had dropped to 0.112 per cent. in seven hours, but was still 23 per cent. above normal.

There was only a very slight increase in the total blood fat in two and one-half hours, but a nine per cent. increase above normal existed after seven hours.

The cholesterol first remained constant and then dropped 13 per cent. below normal in seven hours.

The lecithin showed a decrease from the start and remained about constant at nine per cent. below normal.

Table VIII gives the results obtained under the combined influence of morphine and fat. The carbon dioxide increased somewhat under the influence of morphine during the preliminary period but under the combined influence of morphine and fat during the second period it had dropped three per cent. below normal. The sugar increased 72 per cent. under the influence of morphine alone. Under the influence of morphine

plus fat this increase was still 39 per cent. above normal. The total blood fat increased ten per cent. under the influence of morphine during the first period, but under the influence of morphine plus fat it increased 64 per cent. The cholesterol was not much influenced by fat ingestion plus morphine.

Table IX gives the influence of the ingestion of large quantities of fat alone on the chemical composition of the blood. There is a drop in the carbon dioxide combining capacity of the blood plasma. If we base the average relative increase in the blood sugar on all experiments given in Table IX, it is found to be 14 per cent., but if we omit the last two which show no change in blood sugar, due probably to the fact that the dog would take only 100 cubic centimeters of olive oil, this average increase is 22.5 per cent. There is an increase of 53 per cent. in the total fat. The non-protein nitrogen decreased 25.4 per cent., and the hydrogen ion concentration, 23 per cent .

3. DISCUSSION OF MORPHINE AND FAT STUFFING EXPERIMENTS.

The fact that the carbon dioxide capacity of the blood plasma at the end of two and one-half hours was relatively increased seven per cent. more than the oxygen capacity is of interest in connection with its effect on the oxidations taking place in the body. At the end of seven hours the carbon dioxide capacity had increased further and the oxygen capacity had dropped below normal, thus giving a relative difference of 21 per cent. between these two. This would tend to retard oxidation and favor the formation of products of incomplete oxidation. Higgins and Means⁹², basing their statement on a few experiments on a man under morphine showing a low respiratory quotient, thought this to be proof of a formation of sugar from fat. That these compounds formed are not acetone bodies may be deduced from the fact that there is no acidosis, since the carbon dioxide capacity of the blood is increased.

The sugar increased 53 per cent. during the first two and one-half hours under morphine, but was only 23 per cent. above normal at the end of seven hours (Table VII). The total blood fat showed very little change at the end of the first period, but at the end of seven hours the blood fat had in-

creased nine per cent. It is, of course, impossible to say whether the fat used to form glucose would come from blood fat, in which case the blood fat should be decreased, or whether it would come from fatty depots of the body, or both. One would expect the maximum production of sugar from fat to occur at the time of the maximum change in the relation between the carbon dioxide and oxygen capacities.

The results presented in Table VIII are difficult to interpret because of the two influences, i.e., morphine and fat, operating at the same time. Since there is no appreciable acidosis, many possible sources of the sugar are eliminated. However, Woodyatt^{73b} and others have pointed out that the ingested fat simply replaces body fat in metabolism and does not affect the total fat metabolism; therefore, one should not expect different end products, provided the body fat is still present in sufficient quantity. Since the dogs had ample supplies of body fat, the results presented in Table VIII should not differ materially from those in Table VII when morphine alone was given.

All the results except the last two, presented in Table IX, show a decided increase in blood sugar after giving fat. The amount of fat given in the last two experiments of the table was not so great as in others. Since all experiments, including the last two, show an acidosis, this factor is probably not the cause of the increased blood sugar.

Woodyatt^{73b} points out that 100 gm. of fat in the process of its digestion and intermediate metabolism in the body may furnish 10 gm. of glycerol which is capable of transformation into glucose gram for gram, and he assumes that in diabetes this takes place, but offers no evidence to support this claim. Lusk^{43a} denies the possibility of this transformation in the case of phlorizinized and diabetic animals.

The production of sugar from fat in hibernating animals, in animals under the influence of morphine and fat, and under the influence of fat stuffing alone, does not necessarily have any relation to the possibility of this transformation taking place in the phlorizinized and diabetic animals, since the change in function involved seems to be the oxidative mechanism, which is not the function involved in either phlorizin poisoning or in diabetes. The lowering of the permeability of the kidney to sugar is usually considered as the immediate cause

of phlorizin glycuressis, and the impairment of the internal secretion of the pancreas is usually accepted as the explanation of both experimental diabetes and diabetes mellitus.

While from these last experiments, I cannot claim proof of a definite formation of sugar from fat, they strongly corroborate the more positive findings in the other work.

X. GENERAL SUMMARY.

1. When the glycogen reservoirs of the body are low the ingestion of meat in large quantity results in the deposition of glycogen.

2. The continued ingestion of much meat brings about the retention in the body of a pabulum consisting partly of glycogen and partly of fat. Only when meat in very great excess is given is fat alone retained.

3. Morphine depresses the oxidative processes in the body.

4. The opinion that fat is transferred into sugar under the conditions given in No. 3 is supported.

5. When fat alone is given to a dog in large quantities there is an increase in the blood sugar.

6. The increase in sugar under the conditions given in No. 5 also supports the opinion that fat can be transformed into sugar.

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THE IMMEDIATE INFLUENCE OF ALCOHOL INGESTION UPON DIABETIC GLYCOSURIA AND BLOOD SUGAR.

By L. S. FULLER, M. D.

From the Physiatrie Institute, Morristown, New Jersey.

It has been shown by Allen and Wishart¹ and Leclercq² that alcohol, added to the diet of severely diabetic patients in such quantities as to raise the caloric intake above the caloric tolerance, is responsible for a gradual development of glycosuria or hyperglycemia. Therefore, though not directly convertible into either sugar or acetone in the organism, it follows the same law as all other known sources of energy, in that it cannot serve as a means to fatten or strengthen diabetic patients beyond the limits set by the severity of their diabetes, but, on the contrary, attempts in this direction merely result in bringing the contrary, attempts in this direction merely result in bringing back active diabetic symptoms. The literature quoted in the former of the papers mentioned indicates that alcohol has no direct action, like that of carbohydrate, in preventing the production of acetone bodies. On the other hand, certain of the earlier writers have reported a temporary reduction of glycosuria by alcohol in a type of diabetic cases which are now recognized as mild, and Allen and Wishart observed a fall of blood sugar during several hours after alcohol ingestion in certain cases. It is thus possible that the diminished ketonuria sometimes described as the result of giving alcohol to diabetics may receive a simple physiological explanation. If the alcohol is substituted for fat in the diet, such a result may be expected from the replacement of a ketogenic by a non-ketogenic material in metabolism. If the alcohol is merely added to the previous diet, a saving of sugar by a lessening of glycosuria might explain the reduced ketogenesis. Some observations were therefore undertaken to determine the actual immediate effect of alcohol administration upon diabetic hyperglycemia and glycosuria. For this purpose, patients were selected who either had stubborn hyperglycemia on a given diet, or were in mild or severe stages of glycosuria. No tests of ketogenesis were included, because the only available patient with continuous and regular ketonuria was a child,

who could not take alcohol well. Diets were calculated from standard tables, and sugar analyses were performed by the methods of Benedict. In the experiments, 95 per cent. alcohol was given diluted with water, in quantities short of producing unpleasant symptoms.

TABLE I.

*Influence of Alcohol upon Blood Sugar.**Case No. 2014.*

A case of moderate severity in a woman 46 years old and of 10 years duration, with a complicating gangrene, without glycosuria but with moderate hyperglycemia. 20cc. of alcohol diluted with water was given immediately after the fasting blood specimen was obtained.

	Control day. Plasma sugar mg. per 100cc.	Alcohol day. Plasma sugar mg. per 100cc.
Fasting.....	242	189
First hour..	238	182
Second hour	250	156
Third hour..	234	164

Case No. 630.

A woman 47 years old with diabetes of 6 years duration and moderate severity, running a constant hyperglycemia, but with no glycosuria. 20 cc. of alcohol was given.

	Plasma sugar mg. per 100cc.
Fasting.....	270
30 minutes.....	238
60 ".....	220
90 ".....	206
120 ".....	195

Case No. 1072.

A severe case of diabetes in a man 48 years old complicated by a far advanced pulmonary tuberculosis. 30 cc. of alcohol was given.

	Plasma sugar mg. per 100cc.
Fasting.....	536
First hour.....	625
Second hour....	625
Third hour.....	625

Case No. 1060.

A case of moderate severity in a man 45 years old. The case was fairly well under control at the time of observation. 30 cc. of alcohol was given.

	Plasma sugar mg. per 100cc.
Fasting.....	171
30 minutes.....	171
60 ".....	148
90 ".....	148

Case No. 1054.

A case of considerable severity of $3\frac{1}{2}$ years duration, in a woman aged 41 years, having a persistent hyperglycemia without glycosuria.

	Control day. Plasma sugar mg. per 100cc.	Alcohol day. Plasma sugar mg. per 100cc.
Fasting.....	375	366
First hour..	405	255
Second hour	349	260
Third hour..	416	275

Case No. 1055.

A woman 68 years old with a long standing and severe diabetes, running a constant hyperglycemia. She was given only 15 cc. of alcohol.

	Plasma sugar mg. per 100cc.
Fasting.....	255
30 minutes.....	255
60 ".....	226
90 ".....	187

Case No. 784.

A case of very severe diabetes in a boy 7 years old. Only 5 cc. of alcohol was given.

	Plasma sugar mg. per 100cc.
Fasting.....	555
First hour.....	469
Second hour....	536
Third hour.....	536

Patients No. 1054 and 2014 were tested on days of plain fasting in comparison with days on which alcohol was given, as shown in Table I. A distinct reduction of blood sugar is evident on the alcohol days. The other alcohol tests in this table were conducted without controls. It was known from general experience with these cases that their hyperglycemia was continuous and stubborn, so that it was little changed by as much as 24 hours of fasting. Any observed fall of blood sugar could therefore be attributed with reasonable probability to the alcohol. Such a fall was evident in three of the cases (Nos. 630, 1055, 1060). A slight fall may have been produced in another case, namely, No. 784, though this small change was probably accidental. In case No. 1072 an actual rise of plasma sugar concentration occurred. This difference in response corresponds to definite differences in the character of the cases. The last two mentioned were of very severe type. The absence of any important reduction in one of these and an actual rise of blood sugar in the other following alcohol ingestion seem to be characteristic of severe cases. All of the other cases were moderate in degree. The patients were above 40 years of age, and the condition was readily controllable by diet, even though hyperglycemia was persistent during the period in question. In such cases the effect of alcohol in depressing blood sugar seems to be most readily apparent.

TABLE II.
Case No. 531.

DATE	Wt. 1922 lb.	DIET					URINE				BLOOD	
		Protein gm.	Fat gm.	C. H. gm.	Alc. gm.	Total Cal.	Vol. cc.	Quantitative Dextrose	T. N. gm.	NH ₃ -N gm.	Plasma sugar mg. per 100cc. A. M. P. M.	
Feb.												
25	86	50	97	5	—	1100	2750	0	9.8	1.96	230	211
26	—	50	97	5	—	1100	1880	0	6.8	1.72	206	220
27	83	50	97	5	—	1100	1940	0	6.2	1.88	211	209
28	—	65	97	15	—	1200	1990	0	7.1	2.22	243	312
March												
1	83	65	97		—	1200	950	0	7.2	1.93	246	326
2	—	70	104		—	1300	1830	0	7.2	1.97	365	341
3	84	70	104	20	—	1300	1205	0	8.5	2.81	295	366
4	—	70	104	20	76	1832	2195	0	6.7	3.09	357	357
5	86	70	104	20	—	1300	1090	0	11.9	3.03	341	441
6	—	70	104	20	—	1300	2100	0	7.7	2.99	375	469
7	90	70	104	20	—	1300	2000	0	7.9	2.03	366	518

Table II is the record of a woman aged 52, with diabetes of 15 months duration. Notwithstanding the patient's age, this case was of a severe type, somewhat resembling typical youthful cases, and after prolonged treatment the food tolerance was still so low that a diet of 1100 to 1300 calories produced marked hyperglycemia, increasing as the diet was increased. Only the high degree of renal impermeability for sugar prevented glycosuria during this period. On March 4, 76 grams of alcohol was added to the previous diet of 1300 calories, thus raising the ration for this day to 1832 calories. The plasma sugar on this day was identical for morning and evening. As the relations on other days were somewhat variable, no precise influence of the alcohol can be recognized. There was a distinct fall of total nitrogen output on the alcohol day, with a marked compensatory rise the following day. The ammonia excretion was decidedly increased both on the alcohol day and on the following days.

TABLE III.
Case No. 874.

DATE	Wt. lb.	DIET					URINE				BLOOD	
		Protein gm.	Fat gm.	C. H. gm.	Alc. gm.	Total Cal.	Vol. cc.	Quantitative Dextrose	T. N. gm.	NH ₃ -N gm.	Plasma sugar mg. per 100cc.	A. M. P. M.
March												
12	—	70	124	50	—	1600	2960	5.6	7.16	0.99	429	—
13	107	70	124	50	—	1600	3330	6.11	7.17	1.15	—	445
14	—	70	124	50	—	1600	3350	6.92	7.20	1.30	429	—
15	110	70	124	50	—	1600	3450	6.32	7.22	0.92	429	326
16	—	70	50	50	95	1600	3500	—	8.69	0.98	375	270
17	109	70	124	50	—	1600	2650	—	8.53	0.71	334	270
18	—	70	124	50	—	1600	3550	3.65	8.74	1.49	334	300
19	109	70	124	50	—	1600	3200	3.22	7.66	1.07	—	295
20	—	70	124	50	—	1600	3190	3.21	7.84	1.53	375	—
21	110	70	124	50	90	2230	3320	0.22	8.38	1.73	395	189
22	—	70	124	50	90	2230	2910	0.23	7.74	0.95	334	238
23	110	70	124	50	—	1600	2220	2.37	8.82	0.50	326	326
24	—	70	124	50	—	1600	2910	3.57	5.93	0.79	441	385
25	112	70	124	50	—	1600	2920	4.69	6.54	1.08	—	—

Table III. gives the record of a woman aged 55, with arterial hypertension accompanied by mild diabetes and a stubbornly persistent hyperglycemia. On a constant diet, as shown in the table, she was excreting fairly constant amounts of sugar and nitrogen daily. The blood sugar was analyzed twice daily, once in the morning before breakfast and again about 5:00 P.M.

before the evening meal and about 4 hours after the noon meal. It so happened that the afternoon values were frequently lower than those in the morning. On March 16, 95 gm. alcohol was added to the diet in substitution for fat, the intake of protein, carbohydrate and total calories thus remaining unchanged. The alcohol, diluted with water, was distributed in small quantities throughout the day, both with and between meals. The most striking result was that glycosuria ceased abruptly on the alcohol day and then ran at a much lower level on the subsequent days. The plasma sugar concentration was lower on the alcohol day than previously, and some reduction seemed to be maintained during the following days. On March 21 and 22, 90 gm. of alcohol was given as an addition to the diet, thus raising the calories to 2230 on each of these days. Under these conditions also there was a very marked fall in glycosuria. The plasma sugar on March 21 showed a more decided drop in the afternoon than on any other day of the series, but this change was less marked on March 22. On the following days, after omission of alcohol, both the glycosuria and the hyperglycemia rose. Neither the total nitrogen nor the ammonia excretion was affected by the alcohol in any important degree.

The case represented in Table IV was that of a man aged 37, with an uncomplicated mild or moderate diabetes. On May 19 200 grams of alcohol was given as an addition to the diet, thus more than doubling the former caloric intake. As this quantity proved somewhat uncomfortable, the alcohol was reduced on the following day to 100 grams. No appreciable change in the glycosuria resulted on either of these days. On the following day (May 21) however, the sugar excretion fell sharply to 3.29 gm. May 22 to 24, 100 gm. of alcohol was again added to the diet daily. The sugar excretion on the first day was markedly increased to 12.26 gm., but this increase may have been merely compensatory or delayed excretion from the preceding day. On May 23 the glycosuria was about the average for this patient, but on May 24 a marked fall to 2.9 gm. occurred. This was followed by a distinct increase on the following three days, May 25 to 27. These additions of alcohol to the diet did not appreciably alter the total nitrogen excretion, but on the whole seemed to increase the ammonia output.

TABLE IV.

Case No. 1134.

DATE	Wt. 1922 lb.	DIET					URINE				BLOOD	
		Protein gm.	Fat gm.	C. H. gm.	Alc. gm.	Total Cal.	Vol. cc.	Quantitative Dextrose	T. N. gm.	NH ₃ -N gm.	Plasma sugar mg. per 100cc.	
											A. M.	P. M.
May												
14	120	60	57	60	—	993	2080	6.65	5.22	0.59	—	—
15	—	60	57	60	—	993	2815	7.86	5.75	0.82	—	—
16	120	60	57	60	—	993	3383	12.83	6.67	0.61	295	—
17	—	60	57	60	—	993	3100	10.11	9.14	0.83	—	405
18	129	60	57	60	—	993	2690	7.06	7.53	0.76	265	349
19	—	60	57	60	200	2393	4355	8.86	7.87	1.28	—	334
20	129	60	57	60	100	1693	3215	9.53	6.30	0.87	—	—
21	—	60	57	60	—	993	2105	3.29	8.80	0.46	209	—
22	129	60	57	60	100	1693	2895	12.26	—	—	238	326
23	—	60	57	60	100	1693	3285	6.12	—	1.24	238	300
24	129	60	57	60	100	1693	2820	2.90	6.99	0.82	226	295
25	—	60	57	60	—	993	3645	14.44	9.31	1.14	189	357
26	129	60	57	60	—	993	2295	8.39	7.26	0.57	—	—
27	—	60	57	60	—	993	2330	13.28	8.25	0.79	—	—
28	129	60	57	60	—	993	2810	5.28	6.50	0.86	—	—
29	—	60	57	60	—	993	3550	12.17	6.29	0.54	—	—
30	128	60	16	60	50	974	2930	0	6.11	0.42	—	300
31	—	60	21	60	50	1011	2740	0	6.36	0.48	209	341
June 1	128	60	13	60	50	947	2840	0	5.09	0.50	220	306
2	—	60	32	60	50	1118	1750	0	—	0.58	223	293
3	129	60	25	60	50	1055	1830	0	6.22	0.49	268	—
4	—	60	57	60	—	993	1610	6.18	—	0.48	—	375
5	129	60	57	60	—	993	2075	9.42	6.97	0.48	260	416
6	—	60	57	60	—	993	3055	8.64	7.54	0.71	—	—
7	120	60	57	60	—	993	2600	7.59	6.77	0.73	—	—

May 30 to June 3 inclusive, 50 gm. of alcohol was added to the diet daily in approximate substitution for fat, so that the total caloric intake was only slightly changed. The remarkable feature is that glycosuria remained entirely absent during this period and reappeared in its former amounts afterward. The total nitrogen and also the ammonia excretion seemed slightly reduced during this time, though the change is within the limits of accidental variation.

The changes in blood sugar were less marked than those in the urinary sugar. The evening analyses were regularly higher than those in the morning on the days with and without alcohol. On the whole, changes in glycosuria are not adequately accounted for by the alterations of blood sugar, so that a possible reduction of renal permeability seems indicated.

The patient whose record is shown in Table V. was a boy aged 8, with diabetes of 26 months duration and unusual se-

TABLE V.
Case No. 784.

DATE 1922	Wt. lb.	D I E T					U R I N E			
		Protein gm.	Fat gm.	C. H. gm.	Alc. gm.	Total Cal.	Vol. cc.	Quantitative Dextrose	T. N. gm.	NH ₃ -N gm.
February										
24	—	60	60	6	—	804	1110	20.7	5.88	3.88
25	34	60	60	6	—	804	2330	21.8	5.73	3.01
26	—	60	60	6	—	804	3010	24.9	8.68	4.07
27	34	60	60	6	—	804	1690	18.1	6.89	3.21
28	—	60	60	6	—	804	1620	26.4	9.02	2.42
March 1	33	60	60	6	—	804	2310	27.5	9.70	3.64
2	—	60	60	6	—	804	2690	41.3	9.17	3.64
3	33	60	60	6	—	804	2110	34.4	10.97	2.49
4	—	60	60	6	33	1035	3800	41.0	8.81	4.45
5	33	60	60	6	—	804	2350	39.6	7.25	4.27
6	—	60	60	6	—	804	2590	40.3	9.99	3.97
7	32	60	60	6	—	804	2750	29.9	10.23	3.92
8	—	60	60	6	—	804	3380	38.4	9.61	4.50
9	32	60	60	6	—	804	3050	37.0	9.00	4.41
10	—	60	60	6	—	804	2830	48.5	9.00	4.92
11	30	60	34.3	6	33	804	2040	32.8	8.13	4.74
12	—	60	60	6	—	804	2630	54.3	7.46	3.35
13	31	60	60	6	—	804	2131	41.4	10.74	3.85
14	—	60	60	6	—	804	—	—	—	—
15	32	60	60	6	—	804	6523	42.2	7.15	3.26

verity. For some time after first coming for treatment he had shown "total" dextrose-nitrogen ratios, and though these fell somewhat under treatment, it was never possible at any time to abolish the glycosuria. Heavy glycosuria and ketonuria were continuous on the diet shown. As the boy became nauseated and unwell from taking much alcohol, tests were possible only on the two days shown in the table. On March 4, 33 gm. of alcohol was added to the diet, thus raising the ration from 804 to 1035 calories. No effect upon the glycosuria was perceptible. A lowering of the total nitrogen excretion seemed probable on this and the following day, while a definite increase of ammonia output was also present. On March 11, 33 gm. of alcohol was given in substitution for the caloric equivalent of fat. The glycosuria on this day was appreciably reduced. A fall in the total nitrogen excretion is suggested on this and the following day, but no appreciable change of ammonia elimination occurred.

This experiment shows no antiketogenic influence of alcohol as far as can be judged from the ammonia analyses.

On the contrary, a slight increase of ammonia was noted in the first test when alcohol was given as an addition to the diet. The usual negative influence upon the glycosuria in a severe case was observed when alcohol was thus added; but on the other hand, in the substitution test, alcohol showed its usual lower glycosuric effect as compared with fat. No blood sugar analyses were performed in this experiment.

TABLE VI.

Case No. 1132.

DATE 1922	Wt. lb.	DIET					URINE				BLOOD	
		Protein gm.	Fat gm.	C. H. gm.	Alc. gm.	Total Cal.	Vol. cc.	Quantitative Dextrose	T. N. gm.	NH ₃ -N gm.	Plasma sugar mg. per 100cc.	
											A. M.	P. M.
May 7	—	60	51	50	—	900	925	4.74	850	0.74	—	—
" 8	88	60	50	50	—	900	2025	15.99	8.26	0.48	—	—
" 9	—	60	51	50	—	900	2435	5.70	9.14	0.58	—	—
" 10	88	60	51	50	—	900	1100	5.24	4.33	0.35	—	319
" 11	—	60	51	50	—	900	1785	15.04	5.62	0.54	—	300
" 12	88	60	51	50	—	900	2110	10.9	8.48	0.55	300	500
" 13	—	60	51	50	100	1600	1475	9.07	4.83	0.52	280	366
" 14	88	60	51	50	100	1600	2340	5.47	7.13	0.55	280	441
" 15	—	60	51	50	100	1600	2158	9.17	6.31	0.45	341	405
" 16	88	60	51	50	100	1600	2242	6.27	5.59	0.47	300	300
" 17	—	60	51	50	100	1600	2063	10.93	5.44	0.40	334	395
" 18	88	60	51	50	—	900	2320	22.96	8.83	0.77	375	484
" 19	—	60	51	50	—	900	1355	15.31	6.11	0.46	375	577
" 20	88	60	51	50	—	900	1875	4.25	—	0.67	—	—
" 21	—	60	51	50	—	900	767	0.09	4.24	0.48	357	—
" 22	88	60	51	50	—	900	1410	7.44	—	—	—	—
" 23	—	60	51	50	—	900	1050	2.01	7.58	0.36	357	—
" 24	88	60	51	50	—	900	1375	0.93	5.29	0.47	—	—
" 25	—	60	18	50	44	900	3050	neg.	11.3	1.10	—	250
" 26	88	60	16	50	42	900	1490	neg.	6.07	0.55	162	341
" 27	—	60	25	50	33	900	1665	2.44	5.52	0.74	130	265
" 28	88	60	20	50	40	900	1920	neg.	5.83	0.55	192	—
" 29	—	60	29	50	28	900	1380	neg.	4.13	0.38	210	234
" 30	87	60	51	50	—	900	1690	neg.	5.20	0.24	—	—
" 31	—	60	51	50	—	900	1480	neg.	6.65	0.43	—	—
June 1	86	60	51	50	—	900	1845	neg.	7.31	0.61	—	—
" 2	—	60	51	50	—	900	2030	neg.	—	0.60	—	—
" 3	86	60	51	50	—	900	—	—	—	—	—	—
" 4	—	60	51	50	—	900	—	—	—	—	123	—
" 5	88	70	77	30	—	1100	—	—	—	—	—	—
" 6	—	70	77	30	—	1100	—	—	—	—	—	—
" 7	88	70	77	30	—	1100	—	—	—	—	075	—
" 8	—	70	77	30	—	1100	—	—	—	—	—	—
" 9	88	70	100	30	—	1300	—	—	—	—	—	—
" 10	—	70	100	30	—	1300	—	—	—	—	106	—

The case represented in Table VI. was one of moderately severe diabetes of 3½ years duration in a man aged 29 years.

A fluctuating glycosuria was present on the diet of 60 gm. protein, 50 gm. carbohydrate and 900 calories, without ketonuria. May 13 to 17, 100 gm. of alcohol was given as an addition to the diet, thus raising the ration to 1600 calories daily. No important change in the glycosuria resulted. The plasma sugar on May 16 was identical for morning and evening. On the other alcohol days it was higher afternoons than forenoons. Nevertheless a distinct influence of the alcohol is perceptible, inasmuch as the afternoon values were definitely lower during the alcohol period than on the days before or after. A slight fall in total nitrogen output occurred during the alcohol period, with no subsequent increase. The ammonia output was not appreciably altered.

May 25 to 29, quantities of 28 to 44 gm. of alcohol were given daily in substitution for fat, so as to keep the ration of 900 calories unchanged. The glycosuria, which by this time was low, ceased with the first alcohol day. There was a slight return on May 27, but sugar then remained absent both during and after the alcohol period. The sudden rise of both nitrogen and ammonia elimination on the first alcohol day is difficult to explain; otherwise the output of these substances seemed little affected. The plasma sugar was higher afternoons than forenoons.

On the whole, little difference between alcohol and fat is perceptible in this experiment. The patient was gaining tolerance on the undernutrition diet, as shown by the diminishing glycosuria and the ability to assimilate higher diets with normal blood sugar soon afterward.

CONCLUSION.

The immediate effect of alcohol is to reduce both hyperglycemia and glycosuria in most cases of mild or moderate diabetes. This effect is most pronounced when the alcohol is substituted for the caloric equivalent of fat, but is also frequently manifest when the alcohol is given as an addition to the previous diet. These effects are usually lacking in diabetic cases of great severity.

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EXPERIMENTAL STUDIES IN DIABETES.

SERIES II. THE INTERNAL PANCREATIC FUNCTION IN RELATION TO BODY MASS AND METABOLISM.*

10. THE INFLUENCE OF THE THYROID UPON DIABETES.

By FREDERICK M. ALLEN, M. D.

*From the Hospital of the Rockefeller Institute for Medical Research,
New York.*

The writer previously¹ reviewed the literature of this subject up to 1913. This literature comprised some of the early clinical reports of the association of glycosuria or diabetes with hyperthyroidism, and the production of glycosuria in normal persons by overdosage with thyroid preparations; also the high carbohydrate tolerance of most cases of myxedema or cretinism, and the lowering of this tolerance by thyroid treatment. Experimentally thyroidectomy with preservation of the parathyroids was stated by various authors to raise the sugar tolerance of normal animals and to reduce the glycosuria following pancreatectomy or epinephrin injections. Histologic changes in the thyroid following removal of the pancreas or in the pancreas following removal of the thyroid have been reported without convincing demonstration. The facts, as far as valid, were all open to a simple criticism of interpretation, namely, that though glycosuria might be partially suppressed by the metabolic injury of thyroidectomy, no evidence had ever been brought to indicate any actual benefit in the form of restoration of the power of utilizing sugar; on the contrary, diabetic symptoms were merely replaced by cachexia and the animals died more quickly with than without thyroidectomy.

* The first four papers of this series were published in the *American Journal of the Medical Sciences*, Vol. 160, 1920, p. 781, and Vol. 161, 1921, pp. 16, 165, and 350. Papers 5 to 9 were published in the *American Journal of Physiology*, Vol. 54, 1920-1921, pp. 375, 382, 425, 439, and 451. Papers 11 and 12, completing the series, will be published in subsequent issues of the JOURNAL OF METABOLIC RESEARCH.

A considerable literature which has accumulated since that time may be partially reviewed under the following heads:

EXPERIMENTAL: A. *Thyroid administration in normal animals.*

B. *Thyroidectomy in normal animals.*

C. *Thyroidectomy in diabetic animals.*

CLINICAL: A. *Carbohydrate metabolism in thyroid disorders.*

B. *Association of thyroid disorders with diabetes.*

C. *Thyroid operations in diabetic patients.*

EXPERIMENTAL.

A. *Thyroid Administration in Normal Animals.*

The earlier attempts with thyroid feeding of normal animals gave varying results. Some features of clinical hyperthyroidism have thus been reproduced in the successful cases, but a more accurate and effective means has been afforded by Kendall's² discovery of thyroxin. Its injection into dogs, goats and other species has produced toxic symptoms and increased metabolic rate. According to Plummer³, the condition of human patients with thyroid adenoma and accompanying simple excess of thyroid secretion is thus imitated. Genuine exophthalmic goitre has not been produced in animals by feeding or injection of normal thyroid substance or extract. Doubt exists concerning claims, such as that of Klose, Lampé and Liesegang,⁴ that the injection of goitre juice from human exophthalmic cases reproduces in animals the entire picture, including exophthalmos, nervous symptoms, tachycardia, elevated temperature, sweating, falling hair, hyperglycemia and glycosuria.

Cramer and collaborators^{5a} demonstrated that thyroid feeding lowers the glucose tolerance of normal dogs, also^{5b} that it causes complete or almost complete loss of liver glycogen in cats and rats, even when the animals are kept on carbohydrate-rich diet. No glycosuria occurs, and the respiratory quotient shows a high and prolonged elevation, indicating a very active combustion of carbohydrate. They conclude that the

thyroid inhibits the formation of glycogen; also, that deficiency of glycogen formation is thus excluded as an explanation of glycosuria. Parhon⁶ found that thyroid feeding of rabbits reduced the liver glycogen as low as one-sixth of the quantity found in control animals, but did not cause it to disappear. The muscle glycogen was not reduced, and the respiratory quotient held the high level characteristic of carbohydrate diet. The suggestion was offered that the deficiency of liver glycogen may have been due to the muscular activity of the thyroid-fed animals, which were very nervous, with trembling legs and ears. Kuriyama,⁷ feeding large quantities of fresh thyroid to rabbits and rats, found a marked reduction in liver glycogen, which was independent of diet, and which persisted after such parenteral doses of glucose as quickly increased the glycogen of normal controls. Neither species showed glycosuria or hyperglycemia from the thyroid dosage, and the tolerance of rabbits for glucose parenterally was not lowered. The sensitiveness to glycosuria and hyperglycemia from epinephrin was also not appreciably changed. The epinephrin content of the adrenals of thyroid-fed rats was not altered. Horrisberger⁸ proved that thyroid feeding increased the metabolism of phlorizinized white rats in the same manner and degree as in controls without phlorizin, thus opposing the view that the metabolic increase is due to lack of the sparing action of carbohydrate. Abelin and Jaffé⁹ discovered that phenylethylamin and tyramin behave similarly to thyroid extract in increasing total metabolism, reducing liver glycogen and raising the respiratory quotient.

Kojima¹⁰ described enlargement of the pancreas and mitoses and other changes in its acinar cells in thyroid-fed rats, and these findings were confirmed by Hoshimoto¹¹. An explanation is difficult, as Kojima still obtained these results when the thyroid extract was boiled. He found no changes in the islands, and there are no reliable reports of changes in them from thyroid administration.

B. *Thyroidectomy in Normal Animals.*

No apparent disturbance of health follows thyroidectomy in adult dogs, at least for several months after the operation. The acute death formerly considered as the rule is now known

to be due only to loss of the parathyroids. The sparing of two or more parathyroids is considered a safeguard against any recognisable parathyroid deficiency. The removal of the thyroid alone, however, causes abnormalities of development in puppies; also, the fatal cachexia described by earlier authors¹² many months after thyroidectomy in adult dogs seems not explainable by any known parathyroid defect, and a doubt is thus raised whether dogs can actually live indefinitely without thyroids. Eppinger, Falta and Rudinger¹³ discovered that the nitrogen excretion of a fasting thyroidectomized dog quickly falls to a lower level than that of a normal fasting animal, and this level cannot be further reduced by fat or carbohydrate feeding. Their report that the excessive nitrogen excretion of depancreatized dogs is reduced by thyroidectomy was corroborated by Lusk¹⁴ with a similar observation in phlorizin glycosuria.

The place assigned to the thyroid by Eppinger, Falta and Rudinger and their followers in their pluriglandular speculations has been sufficiently discussed heretofore¹. Among their claims were assertions that thyroidectomy raises the tolerance of animals for test doses of glucose, prevents glycosuria from epinephrin or the Bernard puncture, and appreciably mitigates the effects of pancreatectomy. Lorand¹⁵ had previously alleged that thyroidectomy two days after pancreatectomy abolishes the glycosuria; also that pancreatectomy is followed by signs of over-function of the thyroid, and that thyroidectomy gives rise to hypertrophy of the islands of Langerhans. This finding regarding islands was supposedly confirmed by Falta and Bertelli¹⁶. The present writer had the opportunity of studying the pancreas of one of Janney's dogs which had been thyroidectomized several months previously, and is convinced of the absence of any variation from the normal structure.

Excluding early experiments in which parathyroids were removed along with thyroids, the increase of glucose tolerance in thyroidectomized animals has in general been confirmed by later writers. McCurdy¹⁷ observed such an increase, using the Blumenthal method of single intravenous injections, thus ruling out the factor of intestinal absorption but not the possibility of an altered renal threshold. McLean¹⁸ stated that the hearts of thyroidectomized rabbits utilized less glucose than

those of normal rabbits in perfusion experiments by the Locke method, but as only a brief preliminary report was published without sufficient record of details, and as the method employed was so uncertain and the results so contradictory to those of others, this work may be dismissed as inaccurate or misleading. Janney and Isaacson¹⁹ found that hypoglycemia is the rule in thyroidectomized dogs, and that the rise of blood sugar after administration of glucose by stomach is delayed as compared with normal dogs. The percentile rise, in comparison with the preceding hypoglycemia, is greater than in normal animals, but the absolute level of blood sugar remains lower than in the normal controls. The question of delayed alimentary absorption was tested by feeding meat and demonstrating practically identical rates of nitrogen excretion before and after thyroidectomy.

The assertion that epinephrin injections produce no glycosuria in thyroidectomized animals was disproved by Underhill²⁰. Böe²¹ found the same hyperglycemia from adrenalin injections in rabbits before and after thyroidectomy. The statement of some authors that the effect of adrenalin is less after thyroidectomy is open to question, because of the variable results of different injections, particularly after repeated doses in the same animal²².

With reference to the cessation of glycosuria in depancreatized dogs after thyroidectomy as reported by Lorand¹⁵, notice must be taken of the fact that the animals were not benefited but their lives were apparently shortened. Similarly MacCallum²³ performed this experiment upon two diabetic dogs. In one the pancreatectomy was not quite complete; glycosuria ceased after thyroidectomy and the animal died in 3 days. The completely depancreatized dog showed merely some reduction of glycosuria after thyroidectomy and died the following day. In the experience of Massaglia²⁴, thyroidectomy performed simultaneously with pancreatectomy did not alter the glycosuria, but when the pancreatectomy was performed several days after the thyroidectomy the sugar excretion was lower than usual. Friedman and Gottesman²⁵ have described disappearance of glycosuria in both partially and totally depancreatized dogs after thyroidectomy. Some of the animals lived for several weeks, but a sufficient demonstration of actual benefit from the thyroidectomy is lacking. The

reduction of nitrogen excretion in normal, depancreatized and phlorizinized dogs alike, as described by Eppinger, Falta and Rudinger and by Lusk, is best interpreted in the sense of a specific influence of the thyroid upon protein metabolism, rather than as an amelioration of the diabetes or evidence of an antagonism between the thyroid and the pancreas.

CLINICAL.

A. *Carbohydrate Metabolism in Thyroid Disorders.*

The most numerous contributions under this head consist of studies of the carbohydrate metabolism by the aid of glucose tolerance tests and blood sugar analyses. It will suffice to mention a series of representative findings in chronological order.

Flesch²⁶ performed 65 tests on 40 patients with Basedow's disease. None of them showed fasting or spontaneous hyperglycemia. After the giving of 100 gm. glucose in tea, 17 out of 28 patients had blood sugar curves above those of normal persons. After partial thyroidectomy, in the early period a still higher number, namely 19 out of 28, reacted with abnormal hyperglycemia, but after passage of a longer time a distinct lowering of the curves was found. Two myxedema patients reacted to the glucose with hyperglycemia equal to that of the hyperthyroid cases. They were treated by implantation of healthy human thyroid tissue, and subsequently exhibited still greater hyperglycemia.

Schulze²⁷ observed glycosuria in 4 out of 16 hyperthyroid patients after ingestion of 100 gm. of glucose. The susceptibility to alimentary glycosuria was found to run parallel with a similar susceptibility to adrenalin glycosuria. The quantities of sugar excreted were always small. The longest and severest cases of hyperthyroidism were the most readily subject to glycosuria. Both glycosuria and hyperglycemia were diminished by partial thyroidectomy.

Geyelin²⁸ found some degree of hyperglycemia (defined as blood sugar above 0.1 per cent.) in 90 per cent. of moderate or severe cases of hyperthyroidism. Glycosuria, either spontaneously or after administration of 100 gm. glucose, was also common. Thyroid treatment raised the blood sugar curve of myxedema patients.

Du Bois²⁹ studied the respiratory metabolism of 11 patients with exophthalmic goitre and 1 cretin. Notwithstanding increased basal metabolism as high as 50 to 75 per cent. above normal, the specific dynamic action of both protein and glucose was within normal limits. The respiratory quotient rose sharply after glucose ingestion, indicating active carbohydrate combustion even in the presence of glycosuria. One patient derived 89 per cent. of his total energy from carbohydrate while excreting sugar in the urine. The conclusion is drawn that the glycosuria in such cases must be explained by abnormal mobilization and not deficient utilization of carbohydrate.

Woodyatt, Sansum and Wilder³⁰, also Wilder and Sansum, using the method of continuous intravenous glucose injections at fixed rates, confirmed the reduced sugar tolerance in hyperthyroidism. As compared with the normal assimilative capacity of about 0.85 gm. of glucose per kilogram per hour, the tolerance in exophthalmic goitre was found to be between 0.5 and 0.7 gm., according to the severity. This reduction of tolerance was regarded as only apparent, due to the fact that the hyperglycogenolysis of hyperthyroidism furnishes an extra supply of endogenous sugar to the organism. The findings contradicted the current belief in an increased sugar tolerance with hypothyroidism. A myxedema patient was found to assimilate glucose only at the normal rate of 0.85 gm. per kilogram per hour. Similarly, patients with hypopituitarism were found able to utilize glucose only at the normal rate, even when the highest dosage by stomach failed to produce glycosuria, the explanation being found in retarded intestinal absorption.

Janney and Isaacson¹⁹ found low blood sugar curves in hypothyroid patients in glucose tolerance tests. In hyperthyroidism the results were mixed; by no means all the curves were high, and the majority were not above normal. A delayed rise of the blood sugar curve was, however, found general in both hypothyroid and hyperthyroid cases. In the latter, the rise was more apt to be superposed upon a high or normal blood sugar level, and in the former it was more apt to be superposed upon an originally subnormal level, thus giving the characteristic peculiarities. Janney and Henderson¹⁹ like-

wise obtained mixed results, less constant than the findings in dogs.

Denis and Aub³¹ found fasting hyperglycemia extremely rare in their cases of hyperthyroidism. An excessive rise of blood sugar after ingestion of 100 gm. glucose and 50 gm. bread was found in every case examined. No regular relation was demonstrable between hyperglycemia and glycosuria on the one hand and the severity of the toxic condition on the other. Improvement of the condition by rest or operation was sometimes accompanied by reduction of the tendency to hyperglycemia. In two cases of hypothyroidism no change in the fasting blood sugar was observed to result from administration of thyroid extract.

Hamman and Hirschman³² reported abnormal hyperglycemia with glucose tolerance tests in hyperthyroid cases, and the curves were often slow in reaching their maximum. In one instance a normal curve was found one month after partial thyroidectomy. Epinephrin caused a high and prolonged rise of blood sugar in hyperthyroid cases.

Lueders³³ found high and prolonged elevation of blood sugar to be the rule in glucose tolerance tests in hyperthyroidism, but the results were not constant.

Sanger³⁴ studied 8 cases of Graves' disease in which the basal metabolism was 30 per cent. or more above normal. After a fast of 14 to 16 hours, each patient drank a glucose solution which generally represented 1.75 gm. per kilogram of body weight. Blood sugar analyses and respiration determinations with the Tissot apparatus were performed at short intervals. Starting with fasting respiratory quotients somewhat lower than those of the normal controls, the hyperthyroid patients exhibited as their most striking characteristic a very rapid rise to a high quotient, approaching or even exceeding 1, and the maintenance of this high level through the 2½ hours of observation, while the quotients of the normal control subjects rarely rose above 0.9 and tended to fall slightly before the close of the experiments. One mild case showed little alteration of glucose tolerance; but the characteristic hyperglycemic response of hyperthyroidism was present in all of the 7 more severe cases, and 6 of these showed glycosuria. It was concluded that the specific dynamic action of carbohydrate was probably the same in the hyperthyroid cases as

in the normal controls, and that the hyperglycemia and lowered tolerance of Graves' disease is due not to inability to utilize carbohydrate but probably to a decreased ability of the liver to store it. Both the hyperglycemia and the exaggerated rate of sugar combustion were interpreted in harmony with Cramer's observations of lack of glycogen formation in the liver with thyroid intoxication.

Morris³⁵ found the glucose tolerance test of confirmative value in the diagnosis of mild or doubtful cases of hyperthyroidism. He found that the blood sugar in the hyperthyroid cases rose higher than normal and returned to a normal level in about 4 hours; the maximal hyperglycemia was reached in 1½ to 2½ hours, while in normal controls it was reached within 1 hour.

Boothby³⁶ concluded from a similar study that "the blood sugar curves following the ingestion of 100 gm. of glucose have not been sufficiently consistent in the different types of cases studied to be of diagnostic value, in spite of the fact that high and prolonged curves were more frequently found in patients with hyperthyroidism than in those with hypothyroidism".

Olmstead and Gay³⁷, using glucose tolerance tests, found a distinction between the hyperglycemic curves of hyperthyroidism and of diabetes, in that the former were high but steep, while the latter were both higher and more prolonged.

B. *Association of Thyroid Disorders with Diabetes.*

Chvostok³⁸ reported alimentary glycosuria in 60 per cent. of his cases of Basedow's disease. Kocher³⁹, somewhat later, also found the combination frequent. It is difficult to determine what proportion among the cases of glycosuria represented actual diabetes, but the latter is evidently rare. The literature of this association is reviewed by Labbé⁴⁰, who states that Gastand in a thesis in 1913 collected a total of 58 instances reported by authors up to that time, and by Fitz⁴¹, who mentions that Billings observed only 1 case of glycosuria among 61 cases of exophthalmic goitre, and that Greeley⁴² found only 6 instances of exophthalmic goitre among 614 diabetics at Waukesha. Labbé described 5 cases of the combination from his own experience, but doubted the rôle of the thyroid in the etiology of the diabetes. Fitz gave an account of 39 previously

unreported examples of the combination, 33 of them from the Mayo Clinic and 6 from the Massachusetts General Hospital. As evidence of the rarity, he stated that only 9 cases of diabetes were found among 1800 cases of exophthalmic goitre in the Mayo Clinic. Because of this reason, and the fact that the diabetes might either precede or follow the thyroid trouble, he concluded that the association is fortuitous. The patients with non-toxic goitre showed no improvement in their diabetes after partial thyroidectomy. Certain patients, on the other hand, with toxic thyroid disease and diabetes, improved considerably in respect to their diabetes after the thyroid intoxication was relieved. This benefit was believed to be sufficiently explained by a reduction of the metabolic rate, acting similarly to a reduction of diet. Some further references to hyperthyroidism in association with diabetes are contained in the paper of Rohdenburg, mentioned below.

According to the testimony of a series of authors, the administration of thyroid substance may not only cause glycosuria in normal persons and reduce the usually high carbohydrate tolerance of hypothyroid patients, but may also stand in suspicious relationship with the onset of true diabetes. Friedrich Müller⁴³ gave thyroid tablets for several weeks to a woman with Basedow's disease. The Basedow symptoms were aggravated, and sugar appeared in the urine in increasing quantities. The glycosuria persisted after the tablets were discontinued; the patient died several months later in diabetic coma. The occurrence of glycosuria in several normal persons after large dosage with thyroid tablets was also recorded by Müller. He further mentioned a physician's wife who had a large goitre for some years and was treated with thyroid tablets. During these years she had continuous glycosuria of 3 to 5 per cent., but it was not known whether this antedated the thyroid treatment or not. In later years the goitre decreased in size and thyroid treatment was stopped, and glycosuria thereafter remained absent, even after eating of the largest quantities of carbohydrate.

Strasser⁴⁴ described a cretin 8 years of age, treated by thyroid feeding beginning in July, and in September polyphagia, thirst, polyuria and glycosuria were present. The thyroid tablets were omitted and diet and codein were tried, but the diabetes went on to termination 17 months later in coma.

One case of diabetes developing after treatment of myxedema by thyroid feeding was seen by Allen, Stillman and Fitz⁴⁵, but study of this case proved that doses of thyroid suitable for treatment of the myxedema were entirely compatible with improvement of the food tolerance, and it seemed probable that the myxedema and the diabetes were independent disorders. Other reports of hypothyroidism associated with diabetes were referred to in the writer's former review¹.

C. Thyroid Operations in Diabetic Patients.

In one sense, Falta's⁴⁶ trial of X-ray treatment of the thyroids of six exophthalmic goitre patients may be considered as the beginning of these procedures. Four of these had diabetes, the others only more or less fatty indigestion as a complication. In Case I (diabetes with steatorrhea), irradiation of the goitre was without effect, and death occurred from diabetes and pyelonephritis. Various autopsy findings are mentioned, but nothing is said of any examination of the pancreas. Case II represented diabetes without fatty stools; irradiation of the goitre was again fruitless. In Case III the diabetes apparently antedated the hyperthyroidism. The slight glycosuria ceased after the second Roentgen treatment of the thyroid. In the fourth instance (Case VI) irradiation of the goitre supposedly cured the diabetes, but the case had been extremely mild from the outset. In the remaining 2 cases the X-ray applied to the thyroid supposedly raised the sugar tolerance. In view of the uncertain efficacy of Roentgenotherapy of the thyroid, and the known influence of hospital care and moderate dietary restriction upon both thyroid disease and mild diabetes, the above evidence must be considered inadequate for establishing any conclusions. In addition, it must be recognized that the combinations represented in these few cases are not typical but are actually rare.

More striking observations in two still more unusual cases have been published by Rohdenburg⁴⁷. One of these occurred in a family with a high hereditary incidence of diabetes. In this connection a chart was shown, illustrating marked increase of diabetic glycosuria from the feeding of either desiccated thyroid or desiccated adrenal glands. After the deaths of three members of this family from diabetes, the son of one

of them, who had been diabetic for some time previously, developed exophthalmic goitre. He then disappeared from observation. After five years he was seen again, and gave a history of complete freedom from diabetic symptoms in consequence of a partial thyroidectomy. Diet restrictions had been discarded, and the author proved that "the consumption of two pounds of grapes and three ice-cream sodas within 12 hours at the time of his visit failed to produce sugar in the urine". The second case reported was that of a patient with exophthalmic goitre, whose father had died of diabetes. One lobe of the thyroid had been removed, with resultant general improvement and gain of 15 pounds' weight. Mild diabetes subsequently developed (glycosuria 1.8 to 2.5 per cent., blood sugar 140 mg. per 100 c.c., cessation of glycosuria within 16 hours of fasting). After 5 days of sugar-freedom, the other thyroid lobe was extirpated, leaving the isthmus. On the day after operation there was glycosuria of 4.8 per cent., which gradually disappeared in the following 4 days. Within a month after operation the patient had gained 25 pounds in weight, hyperthyroid symptoms were absent, and 2 ounces of cane sugar added to a diet consisting entirely of carbohydrate failed to produce glycosuria.

From the surgical treatment of goitre in the presence of a complicating diabetes to the partial removal of a normal thyroid in the attempt to cure diabetes is a considerable step. If Falta and collaborators had had full faith in their own doctrines, they should have adopted the measures for which Crile⁴⁸ actually gained priority some years later. He removed one adrenal and approximately three-fourths of the thyroid, and divided both cervical sympathetic trunks, in a series of patients with supposed injurious preponderance of a group of glands, including one diabetic. Two years after the first of these operations, he described the general results as encouraging. During several months which had elapsed since the operation on the the man with mild diabetes, glycosuria had ceased and a high tolerance had been attained, and at least a share of these benefits was credited to the surgical treatment. In the latest book of Crile⁴⁹ on the thyroid, however, there is no mention of its influence upon carbohydrate metabolism and no advocacy of its resection in diabetes.

O'Day⁵⁰ limited his diabetic surgery to the thyroid. He first

reported two cases of combined diabetes and exophthalmic goitre. One patient was a man aged 24, treated first by injection of boiling water into the thyroid and later by a partial resection. Glycosuria ceased as the symptoms of thyroid intoxication improved, and continued absent when diet was disregarded and sugar and candy eaten. The second patient was a woman with diabetes who subsequently developed exophthalmic goitre. Partial thyroidectomy was followed by acute intoxication and dangerous acidosis; then gradually all symptoms were relieved and a supposedly normal carbohydrate tolerance attained. In a brief note, O'Day stated; "Encouraged by the experience of having several cases of glycosuria associated with exophthalmic goitre clear up when the hyperthyroidism was corrected, two cases of diabetes in young subjects with no goitre symptoms were treated by removing the greater part of the thyroid gland. The results were as follows: One was restored to complete carbohydrate tolerance, the other to a tolerance of nine ounces of carbohydrate per day." This report was published after a few months of observation of these cases, and there has been no further mention of the use of this method by O'Day or other surgeons.

SUMMARY.

It is significant that the general trend of evidence has steadily reduced the supposed rôle of the thyroid in diabetes. The loose early statements of the frequency of glycosuria with clinical hyperthyroidism have not held good. A broad rule with few if any exceptions is that toxic agents lower the apparent assimilation of carbohydrate. It is therefore to be expected that toxic goitres will be associated with more or less lowering of the assimilation, and it is only surprising that this reduction does not run parallel with the degree of intoxication, is lacking altogether in many cases, and in the great majority of cases is so slight that it does not give rise to spontaneous glycosuria and is demonstrable only by the most refined tests. Similarly, poisoning of normal persons or animals by thyroid products may be expected to depress the apparent assimilation of glucose, as judged by slight glycosuria or hyperglycemia, but it is noteworthy that an impairment of combustion in the diabetic sense is proved by the high respiratory

quotients to be absent. The poverty of liver glycogen, whether due to deficient formation or excessive consumption, was rightly interpreted by Cramer as proof that glycosuria and diabetes are not explainable by mere lack of glycogen storage. It has not yet been proved whether this scarcity of liver glycogen is specific to thyroid intoxication or may be found also in other forms of intoxication, as by bacterial toxins, associated with an equal rise of total metabolism. Both the intoxication and the elevation of metabolism may tend to aggravate any existing or latent diabetes, and relief from the intoxication may be expected to benefit the diabetes and perhaps allow it to return to its latent state. On the other hand the combination of hyperthyroidism with diabetes is so rare that it must be considered accidental; the association of diabetes with hypothyroidism is also known; and the onset of diabetes after administration of thyroid tablets is another rarity which may be ranked on a par with the formerly accepted "traumatic diabetes", namely as representing merely the outbreak or the discovery of a preexisting diabetes. The elevation of apparent glucose tolerance produced in normal animals by thyroidectomy is trivial in degree. Thyroidectomy in diabetic animals is best regarded as an additional injury which may to some extent suppress the typical mobilization of sugar; the most important point is the total lack of evidence of the recovery of any of the normal power to burn sugar. Here is another instance of the disastrous confusion between glycosuria and diabetes; as it is incomprehensible that a totally depancreatized animal should regain any of the power of normal sugar utilization which is dependent upon the pancreas, it must be impossible that the removal of any other organ could effect any amelioration of the diabetes in the true sense of the word. The treatment of clinical diabetes by the removal of organs supposedly antagonistic to the pancreas has evidently failed. Altogether, the investigations have contributed a little information concerning the specific function of the thyroid, and have furnished more complete disproof of the imagined opposition between the thyroid and pancreas, and of the hypothetical role of the thyroid in the etiology of diabetes, than existed at the time of the former review.

The writer's experiments in the former publication mentioned¹ consisted in (a) feeding of thyroid to normal animals,

with the result of a trivial lowering of their glucose assimilation, and to partially depancreatized animals, with the result that no diabetes was produced even in animals very close to the verge of diabetes; and (b) partial thyroidectomy (removal of not more than seven-eighths of the thyroid) in diabetic animals, with negative effects upon the diabetes even when considerable portions of the adrenals were also removed. It was desired to repeat the thyroid feeding experiments upon partially depancreatized animals, in order to test the influence both upon pancreatic deficiency which was not quite sufficient to cause diabetes, and also upon the course of an existing diabetes. The previous thyroidectomy experiments had imitated any probable clinical procedures, since it is not likely that any surgeon would contemplate the removal of more than seven-eighths of the thyroid of a human diabetic; but for theoretical information it seemed desirable to make a trial of complete thyroidectomy in dogs with various degrees of diabetes. This line of experimentation might prove instructive in two directions; first in regard to any specific thyroid influence, and second in regard to a possible influence of raising or lowering the total metabolism. The latter point in particular pertains to the general subject matter of this series of papers. The observations will be presented in two groups: I., experiments with thyroid feeding; and II., experiments with thyroidectomy.

I. EXPERIMENTS WITH THYROID FEEDING.

Dog B2-25, male, mongrel, normal weight 18.2 kg., was partially depancreatized on Dec. 16, 1913, so that the remnant left was estimated at $1/12$ to $1/13$ of the gland, as previously described⁵¹. He was kept free from diabetic symptoms by strict undernutrition, and the food tolerance gradually rose in the ensuing months. At first as little as 200 gm. of beef sufficed to cause glycosuria, but by November, 1914, the protein tolerance was so high that glycosuria resulted only when as much as 1400 gm. of beef lung was fed at one time, as described in another place. Beginning Nov. 27, the dog was placed for one week on a diet of 800 gm. cooked beef lung and 200 gm. raw beef thyroid. Neither glycosuria nor any symptoms of hyperthyroidism resulted. The tolerance and

health seemed to be as good on the thyroid diet as on the same quantities of muscle or lung.

Dog B2-43, female, bull terrier mongrel, in consequence of two pancreas operations previously described⁵² reached a condition such that glycosuria resulted from moderate quantities of starch as shown by published tests⁵³, but did not result from the largest quantities of protein that could be eaten. July 21, 1914, a regular diet of 1 kg. of beef lung was begun, the body weight being 9.7 kg. The urine remained normal except on July 28, when a single feeding of bread and soup mixture was given by mistake, with resultant heavy glycosuria. Changes of diet were then made as follows:

Date	Body weight, kg.	DIET			
Aug. 17	9.9	900 gm. beef lung and 100 gm. raw calf thyroid			
" 20	9.9	800	"	"	200 " " "
" 22	10.0	700	"	"	300 " " "
" 25	10.2	500	"	"	500 " " "
" 28	10.3	300	"	"	700 " " "
" 31	10.2				1 kg. " " "
Sept. 2	10.2	1 kg. beef lung.			

Neither glycosuria nor changes in the appearance, behavior, pulse, or general health were observed in consequence of the high thyroid feeding.

As described in the reference cited, on Sept. 10 the feeding of 50 gm. of starch in the form of oatmeal caused no glycosuria, but on Sept. 15 the same quantity of starch in the form of rice produced an excretion of 5.5 gm. of sugar.

In this experiment thyroid feeding failed to produce glycosuria in an animal which was readily subject to glycosuria from starch.

Dog B2-79, male, bull terrier mongrel, normal weight 15 kg., was partially depancreatized on Nov. 10, 1914, the remnant being estimated at $\frac{1}{8}$ of the pancreas. Portions of the record have been given in former publications⁵⁴. The glycosuria which was present on bread feeding ceased on a diet of 1 kg. of beef lung. The earlier published experiments showed how tolerance was gradually lost as the dog was fattened. The diet of 1 kg. raw lung continued from April 7 to May 30, 1915, without glycosuria. Beginning May 30, the diet was changed to

500 gm. lung and 500 gm. fresh sheep thyroid. June 4, the diet of 1 kg. beef lung was resumed, and glycosuria, which had been absent before, appeared to the extent of 0.6 per cent. in 417 cc. of urine on this day. It then remained absent on the same diet to June 26.

On June 26, the diet was changed to 1 kg. of fresh sheep thyroid daily. On July 1 the diet of 1 kg. raw beef lung was resumed. The urine record for this period was as follows:

Date	Urine Vol., cc.	Glycosuria, %
June 26	305	0
" 27	451	0
" 28	452	0.43
" 29	455	2.74
" 30	690	3.70
July 1	777	1.80
" 2	627	4.32

The glycosuria seemed likely to persist on the lung diet, but promptly ceased with a single day of fasting on July 3. Fasting was continued on July 4 and 5 to restore the damaged tolerance. Glycosuria was then absent on 1 kg. of beef lung daily till July 9, when there was a sudden appearance of 2.17 per cent of sugar in 241 cc. of urine. Another 3-day fast was then imposed to stop glycosuria and improve tolerance, and the dog was subsequently used for other experiments.

A possible interpretation of these results seems to be that the glycosuria of June 4 represented a cumulative effect of the preceding thyroid diet; that glycosuria was then absent on the usual kilogram of lung, but was produced within two days by the change to a kilogram of thyroid. As usual when the tolerance is injured, this glycosuria continued after the cause was removed, so that fasting was necessary and the tendency to glycosuria continued for some time on the lung diet formerly tolerated. There were no other perceptible symptoms from the thyroid feeding.

Cat B2-01, a large strong black-and-white female in excellent condition at a weight of 4.1 kg., was partially depancreatized on Feb. 19, 1914. The tissue removed weighed 7.2 gm., and the remnant about the main duct was estimated at 1.8 gm. (1/5). Glycosuria followed, but was checked by fasting and undernutrition. At first the protein tolerance was

limited and heavy glycosuria resulted from any considerable quantities of meat, but by April the animal had become able to live on beef *ad libitum* without excretion of sugar though milk still caused glycosuria. The removal of 0.25 gm. of additional pancreatic tissue on April 21 failed to halt the rise of tolerance, and by the middle of May the cat was able to take 300 cc. milk and as much meat as she would eat daily without glycosuria. This gain of tolerance, though doubtless due chiefly to pancreatic regeneration (the remnant being finally found to weigh 2.6 gm. at autopsy), may have been connected partly with the fall in weight, which now remained almost constant at 3.5 kg.

May 21, the addition of 50 gm. glucose to the usual milk brought back heavy glycosuria. The tolerance was broken down by this program, so that after June 12 the glucose could be omitted and heavy glycosuria continued on a diet of beef and milk. The animal was then kept in a border-line state and used for several experiments, showing the effect of alterations of body weight on the food tolerance. At a weight of 3.3 kg., glycosuria was absent on a diet of 300 gm. lean meat and 300 cc. milk, but it was present even without milk when the weight rose to 4.5 kg.

March 20, 1915, the weight was 2.8 kg., and a diet of 200 gm.

TABLE I. *Cat B2-01.*

DATE 1915	Weight kg.	D I E T	URINE	
			Vol. cc.	Sugar %
May 28	3.5	400 gm. sheep thyroid	225	0.28
" 29		" " " "	210	0.30
" 30		" " " "	235	0.62
" 31		" " " "	405	0.50
June 1	3.6	" " " "	250	0.43
" 2		" " " "	170	0.33
" 3		" " " "	182	0.40
" 4	3.6	" " " "	196	0.18
" 5		400 gm. beef lung	435	0
" 6		" " " "	265	0
" 7		" " " " and 25 cc. milk	425	0
" 8	3.8	" " " " " 50 " "	180	0
" 9		" " " " " 100 " "	215	0
" 10		" " " " " 150 " "	175	0
" 11		" " " " " 200 " "	186	0
" 12		" " " " " 250 " "	210	0
" 13	4.2	" " " " " " " "	290	0.52
" 14		" " " " " " " "	240	0.52
" 15		" " " " " " " "	285	0.77

beef lung was begun. March 30, this was changed to 100 gm. lung and 100 gm. fresh sheep thyroid, and on April 2 to 200 gm. thyroid. Glycosuria remained absent, and the fasting blood sugar on April 6 was 0.095 per cent. The weight had risen to 3.2 kg.

April 9 to 23, the diet was 300 gm. beef lung without thyroid, and the weight rose to 3.5 kg., with no glycosuria. April 23, this diet was changed to 100 gm. lung and 200 gm. fresh sheep thyroid, and on April 26 to 300 gm. thyroid. There was no glycosuria, and the weight remained practically constant. The same condition persisted with a change to 300 gm. lung, May 17-23, and a return to 300 gm. thyroid, May 24-25.

May 26, feeding of 400 gm. thyroid daily was begun, and slight glycosuria appeared May 28. The further results are shown in table I.

The glycosuria continued, and by June 24 had increased to 2.22 per cent. in 240 cc. urine, the body weight being 4.4 kg. Milk was then omitted, but equally heavy glycosuria persisted on the diet of 400 gm. beef lung. By July 1 the glycosuria was 2.86 per cent. in 205 cc. urine, and the weight was 4.3 kg. Continuous fasting from July 1 to 18 was then necessary to stop the glycosuria. This reduced the weight to 3.1 kg. Thereafter a diet was gradually built up, and the cat finally became able again to tolerate 300 to 400 gm. lung daily at about 3 kg. weight.

In this experiment large quantities of thyroid were necessary for any effect, but this was definite when obtained. The glycosuria present on feeding 400 gm. of thyroid was absent on 400 gm. of lung, even with addition of as much as 200 cc. of milk. The thyroid glycosuria remained slight, however, while that resulting from the increase of milk to 250 cc. soon became heavy, and was also harder to stop by fasting. No other symptoms of hyperthyroidism were perceptible, and the body weight increased with increase of the quantity of thyroid fed.

Cat B2-12, adult male, black-and-white, weight 3.8 kg. Nov. 5, 1914, removal of pancreatic tissue weighing 9.7 gm. Remnant left about main duct estimated at 2.6 gm. (a little over $1/5$). Feeding tests up to March, 1915 demonstrated that glycosuria was absent on the largest quantities of meat which the cat

TABLE II. *Cat B2-12.*

DATE 1915	Weight kg.	DIET	URINE	
			Vol., cc.	Sugar %
Mar. 30	3.4	300 gm. lung and 100 gm. thyroid	210	0.60
" 31		" " " " " " "	205	0.28
April 1	3.6	" " " " " " "	110	1.88
" 2		" " " " " " "	200	1.40
" 3		" " " " " " "	156	0.27
" 4		" " " " " " "	170	1.02
" 5		" " " " " " "	237	0.18
" 6	3.8	" " " " " " "	Lost	—
" 7		400 gm. lung	280	0
" 8 to 23		" " "	—	0
" 24 to 26	3.8	200 gm. lung and 200 gm. thyroid	—	0
" 27 to 29		400 gm. thyroid	—	0
" 30 to May 7	3.7	400 gm. lung	—	0
May 8 to 17	3.7	400 gm. thyroid	—	0
" 18 to 24	3.7	500 gm. lung	—	0
" 25 to 31	3.7	500 gm. lung and lard (unweighed)	—	0
Jun. 1 to 7	3.8	500 gm. beef heart and lard	—	0
" 8 to 25	4.5	" " " " " "	—	0
" 26	4.5	" " " " " "	223	0.55
" 27	4.5	500 gm. lung and lard	162	1.22
" 28	4.5	500 gm. beef heart and lard	141	0.50
" 29 to Jul. 2	4.5	500 gm. lung and lard	—	0
Jul. 3	4.5	" " " " "	230	1.42
" 4	4.5	500 gm. thyroid, gradually reduced	197	0.61
" 5 to 14	4.5	to 250 gm. because of growing	—	0
" 15 to 27	3.1	dislike for thyroid	—	0
" 28 to Aug. 4	3.0	500 gm. beef heart	—	0

would eat, but heavy glycosuria could regularly be produced by addition of milk. In March the feeding of meat *ad libitum* was replaced by a fixed diet of 400 gm. beef lung. Table II. gives the record after introduction of fresh sheep thyroid. No blood sugar data were obtained, except a normal figure of 0.10 per cent. fasting on April 6.

This cat failed to show glycosuria at the normal weight of 3.8 kg. or less, on either lung or thyroid feeding. Fattening to a maximum weight of 4.5 kg., by addition of such quantities of lard as the animal would eat, also led to no glycosuria with either lung or thyroid. Beef heart, however, for some reason gave rise to definite glycosuria in the obese animal, but failed to do so after the tolerance was raised by reduction of body weight. As these tests show how close the animal was to the verge of glycosuria, the absence of glycosuria with thyroid feeding represents a very decided negative result in this ex-

TABLE III.

DATE 1917	DOG D4-77				Weight kg.	DOG D4-89				D I E T		
	Blood		Urine			Blood		Urine				
	Plasma Sugar %	Lipemia qual.	Vol. cc.	Dext. gm.		Plasma Sugar %	Lipemia qual.	Vol. cc.	Dext. gm.			
April												
10-11	9.3	—	—	768	0	6.38	—	—	480	0	5.64	300 gm. lung and 100 gm. suet.
11-12	9.5	0.124	0	388	0	4.06	0.086	0	665	0	7.20	Same
12-13	9.4	—	—	250	0	4.58	—	—	624	0	7.18	“ plus 30 two-grain thyroid tablets
13-14	9.3	—	—	540	13.80	7.38	—	—	771	0	6.59	“ plus 50 tablets
14-15	9.3	—	—		5.10	4.10	—	—	770	0	4.34	100 gm. suet and 75 thyroid tablets
15-16	9.2	—	—	386	0	2.38	—	—	540	0	2.04	100 gm. suet and 50 thyroid tablets
16-17		0.204	0	1138	0	3.64	0.116	0	712	0	4.05	100 gm. suet only
17-18	8.9	0.118	Heavy	1220	0	5.40	—	—	778	0	6.94	300 gm. lung, 100 gm. suet and 10 gm. thyroid powder.
18-19		—	—	1720	0	7.40	0.070	0	962	0	8.86	Same
19-20	9.0	0.175	Slight	1916	0	7.20	0.074	0	577	0	3.85	“
20-21		0.208	Faint	1910	6.40	6.32	0.081	0	456	0	5.70	“
21-22	9.2	—	—	1416	7.50	9.06	—	—	340	0	4.93	“
22-23		—	—	1390	+	7.56	—	—	176	0	2.47	“
23-24	9.0	—	—	935	8.60	6.04	—	—	370	0	5.34	“
24-25	9.2	—	—	825	6.19	6.40	—	—	315	0	5.52	“

periment. There were also no other perceptible symptoms of thyroid excess.

Dog D4-77, a small thin black collie mongrel weighing 11 kg., was partially depancreatized on Jan. 19, 1917. The tissue removed weighed 34.6 gm., and the remnant left about the main duct was estimated at 4.3 gm. (1/9). Heavy glycosuria ensued on diets of 500 gm. beef lung or less. By fasting and reduced diet the weight was reduced as low as 7.5 kg. in March. The limits of tolerance were definitely established by repeated tests, and the nutrition was gradually built up by protein-fat diets. Glycosuria always resulted from feeding 500 gm. of lung, but 300 gm. lung and 100 gm. suet appeared to be well tolerated.

Dog D4-89 was a mongrel picked for close resemblance in size and form to serve as a normal control, but was fatter than dog D4-77, so that the initial weight was 15 kg. The opportunity was taken to perform some phlorizin experiments upon D4-89, which subjected this dog to undernutrition and glycosuria somewhat similar to those of D4-77.

April 6 the two dogs, free from glycosuria and weighing respectively 9.2 and 10.7 kg., were placed on a diet of 300 gm. beef lung and 100 gm. suet, with a trifle of talcum powder to prevent diarrhea. Beginning April 10, the urinary nitrogen was determined by Kjeldahl for a preliminary period of 2 days, and then thyroid tablets added to the diet, as shown in Table III. The ordinary commercial 2-grain tablets were used, and were eaten eagerly by both dogs. Glycosuria occurred in dog D4-77 on April 13 and 14, and belated attention was then given to the composition of the tablets, which were found to give a heavy copper reduction, evidently due to milk sugar. The glycosuria ceased with the feeding of 100 gm. suet and 50 thyroid tablets (without lung) on April 14 and 15, and only 100 gm. suet the next day.

A fresh start was made on April 17, with the regular diet of 300 gm. lung and 100 gm. suet, together with 10 gm. of Armour's desiccated thyroid powder, which was labelled as containing 0.2 per cent. iodine and was found free from starch or sugar by test. The experimental results may be summarized under 3 headings.

Diabetic symptoms.—The thyroid dosage produced both

hyperglycemia and glycosuria in dog D4-77, but neither in the normal control D4-89. All blood samples were taken before the day's food was given. The plasma was always clear in dog D4-89, but sometimes showed more or less abnormal turbidity from fat in dog D4-77. There was, however, no apparent relation between this lipemia and the thyroid feeding, and it was probably related only to the diabetic state.

Other symptoms of thyroid excess.—No distinct effect of any kind was noticeable in dog D4-89. The animal was not nervous but may have been slightly unwell. The temperature, taken by rectum several times daily, was regularly between 38° and 38.6°C., while the pulse taken with the animal as quiet as possible varied between 100 and 136. Only once was the temperature found as high as 39° and the pulse 152. There was no consistent increase of urinary nitrogen under thyroid administration. Neither animal was catheterized, and the feces were not analyzed; but the feces were uniformly well formed and apparently well digested, and the record of cage urine indicates fairly regular voiding. The diabetic dog D4-77 was by nature a more nervous animal. A nervous influence of the thyroid dosage was unmistakable, in the form of extraordinary excitability, restlessness, and sometimes tremors. The rectal temperature during the experimental period was between 39° and 39.6°C. The pulse was generally about 164, only once as low as 148. The urinary nitrogen was distinctly increased during the experimental period, but some allowance must be made for the nitrogen of the 10 gm. of thyroid powder. Neither dog showed exophthalmos, and neither lost weight during the experimental period more than could be accounted for by the reduced diet of April 14 to 16.

After-period.—An after-period would have been desirable in the table, to show the effect of simple omission of thyroid upon the sugar and nitrogen excretion, with the diet and other conditions unchanged. It was known from previous experience, however, that a glycosuria which had gained such headway would not stop with simple withdrawal of thyroid on a diet so near the border of tolerance, but on the contrary would quickly progress into hopeless diabetes. Therefore thyroid was discontinued, and 2 fast-days and a day of only 100 gm. suet were used to stop the glycosuria in dog D4-77. The diet of 300 gm. lung and 100 gm. suet was then once more tolerated.

TABLE IV. *Dog E5-19.*

DATE	Time	PLASMA			U R I N E				REMARKS
		Sugar mg. per 100 cc.	CO ₂ vol. %	Corp. vol. %	Vol., cc.	Sugar gm.	Acetone qual.	Total-N gm.	
Nov. 3	—	—	—	—	110	neg.	neg.	2.94	Fed 150 gm. lungs, 100 gm. suet
" 4	—	—	—	—	111	"	"	3.44	" " " " " "
" 5	—	—	—	—	120	"	"	4.30	" " " " " "
" 6	—	—	—	—	100	"	"	3.54	" " " " " "
" 7	—	—	—	—	100	"	"	4.02	" " " " " "
" 9	—	—	—	—	100	"	"	3.56	" " " " " "
" 10	—	—	—	—	130	"	"	4.97	" " " " " "
" 11	—	—	—	—	65	"	"	2.97	" " " " " "
" 12	—	—	—	—	60	"	"	2.66	" " " " " "
" 13	10:15am	179	53.6	35.6	75	"	"	2.53	" " " " " "
	2:15pm	172	59.4	37.5	—	—	—	—	
	6:15pm	116	59.5	31.2	—	—	—	—	
" 14	—	—	—	—	250	"	"	4.44	Same plus 5 gm. thyroid powder
" 15	—	—	—	—	130	"	"	2.66	" " " " " "
" 16	—	—	—	—	200	"	"	5.12	" " " " " "
" 17	—	—	—	—	240	"	"	9.69	" " " " " "
" 18	—	—	—	—	60	"	"	2.11	" " " " " "
" 19	—	—	—	—	330	"	"	6.76	" " " " " "
" 20	—	—	—	—	400	"	"	5.36	" " " " " "
" 21	10:00am	196	67.1	34.5	400	"	"	8.48	" " " " " "
	4:00pm	250	50.0	34.5	—	—	—	—	
	6:00pm	250	64.2	34.6	—	—	—	—	
" 22	—	—	—	—	570	"	"	6.96	" " 10 " " " "
" 23	—	—	—	—	720	"	"	6.40	" " " " " "
" 24	—	—	—	—	630	"	"	5.53	" " " " " "
" 25	—	—	—	—	600	"	"	7.62	" " " " " "
" 26	—	—	—	—	1000	"	"	12.28	" " " " " "
" 27	—	71	51.6	1.4	670	"	"	8.54	Autopsy blood.

Meantime the nervous symptoms subsided and the pulse and temperature returned to the same normal level as in dog D4-89.

It is not certain whether the greater nervous response to thyroid on the part of the diabetic dog in this experiment was due entirely to the more nervous constitution or partly to a sensitive state created by diabetes. The essential feature of the results was the production of hyperglycemia and glycosuria by thyroid in a potentially diabetic dog and the absence of these in a normal dog.

Dog E5-19, a thin brindle female mongrel weighing 10 kg., was partially depancreatized on Sept. 28, 1917. The tissue removed weighed 28.3. The remnant about the main duct was estimated at 2.4 gm. (about 1/13). The resulting diabetes was severe and required stringent undernutrition for its control. When the body weight had been reduced to 9 kg., 200 gm. of lung still caused glycosuria, but a diet of 100 gm. lung and 100 gm. suet was tolerated. Accordingly this was instituted as a regular diet on Oct. 31. The results of the subsequent experimental period are shown in Table IV.

After the preliminary period from Nov. 3 to 13, Armour's thyroid powder, of 0.2 per cent. iodine content, was added to the diet, first in 5 gm. and later in 10 gm. quantity. The dog developed diarrhea, emaciated from an initial weight of 9 kg. to a final weight of 6.5 kg., and died of inanition on Nov. 27.

Glycosuria was not produced, but the higher blood sugar levels during digestion of the regular diet on Nov. 21 as compared with Nov. 13 seem to indicate a definite influence of the thyroid, especially in view of the indigestion and emaciation.

The thyroid feeding failed to cause evident nervourness in behavior, probably because of the weakness. The rectal temperature, instead of being subnormal as usual in cachectic states, was between 38.6 and 39°C. during the period of thyroid dosage. The pulse was generally 164. The dog's skin was noticeably hot to touch.

The urine was passed spontaneously. The elevations of ammonia on Nov. 20, 25 and 26 may have been due to fermentation, which on the whole was successfully guarded against by the use of toluene and sulphuric acid in the bottles. The ex-

cretion of urinary nitrogen was considerably higher after thyroid administration than before. The high figures for Nov. 26 and for the partial specimen on Nov. 27 evidently represent a premortal rise.

It will be noticed that no acidosis was produced in this or other experiments either by the thyroid or by the high fat content of the diet.

At autopsy, the thyroid was found to consist of large vesicles distended with colloid, with their margins thickly beaded with vacuoles (active secretion?). The liver, adrenals and spleen were normal. The kidneys were normal with the possible exception of slight vacuolation of Armanni character in certain tubules. The pancreas remnant was fully normal, and in particular was free from vacuolation or other changes in the islands. Thyroid intoxication thus showed no specific effect upon the pancreatic structure.

II. EXPERIMENTS WITH THYROIDECTOMY.

Dog B2-89 was a yellow female mongrel, aged 4 years, with an initial weight of 13.2 kg., which had been kept under observation in a condition bordering on diabetes and used for various experiments since April 12, 1915. Actual diabetes was produced by the removal of 0.25 gm. additional pancreatic tissue on March 16, 1916. May 18, 1916, both ovaries were removed, as previously described⁵⁵. The diabetes was mild, so that indefinite quantities of protein could be tolerated, as also approximately 150 gm. of bread, but the addition of 75 gm. glucose regularly caused glycosuria of 12 or 13 gm.. The oöphorectomy produced no lasting change in this tolerance.

June 20, 1916, the entire thyroid was removed, with the exception of such tiny shreds as had to be left in order to save three parathyroids with their circulation. The dog quickly recovered from the ether and ate the regular diet on the operative day and the following days. Glycosuria resulted, however, first in traces of 0.2 to 0.3 per cent, but increasing by June 29 to 2.70 per cent. in 380 cc. urine. Therefore, after glycosuria was stopped by a fast-day on June 30, the diet was changed to 100 gm. lung, 100 gm. suet and 50 gm. bread, on which glycosuria remained absent. After July 6 the diet with 150 gm. of bread was again tolerated without glycosuria.

July 27, 75 gm. of glucose was added to the diet, with result-

ing excretion of 9.1 gm. in 217 cc. urine. July 28, the same test was repeated, with excretion of 8.15 gm. in 392 cc. urine.

At the time of the thyroidectomy on June 20, the dog was thin at a weight of 8.3 kg., because of reduced diet, but was strong and lively. After the operation there was increasing indigestion and bulky feces, with corresponding emaciation. At the time of the glucose tests mentioned, the weight was down to 7.0 kg., and the slightly lower glycosuria as compared with former tests is amply explained by the lower weight and poorer food absorption. Glycosuria was absent on the regular diet thereafter, until death from inanition on Aug. 4, at a weight of 6.8 kg.

At autopsy, one small nodule was found at the site of each thyroid lobe, not much larger than a normal parathyroid. These were not examined microscopically, but it was evident that the thyroid had not regenerated to any important extent. With the exception of moderate fatty infiltration of liver and kidneys, the viscera were negative. The pancreas remnant was small, nodular and hard, but when it was cut open the interior was found to be composed of softer tissue. Microscopic examination confirmed the existence of a patchy fibrosis, with interspersed areas of normal appearing acinar tissue. Islands of Langerhans were fairly numerous but small, as frequently found in such a remnant. Their cells were normal and free from vacuolation or any other changes attributable to the thyroidectomy.

The essential feature of this experiment was that the glucose tolerance, though lowered temporarily by the operation (possibly by trauma to the parathyroids), was not increased by thyroidectomy.

Dog D4-62. — This dog, possessing one-tenth of the pancreas, was also previously described in connection with an oöphorectomy which failed to alter the food assimilation⁵⁵. Protein food could be tolerated in maximum quantities, up to 1 kg. of beef lung daily, but the addition of 50 gm. bread sufficed to cause heavy glycosuria. Feb. 3, 1917, the left lobe of the thyroid was removed, leaving the one prominent parathyroid *in situ*. The usual diet of 1 kg. of lung was eaten on this and the following days without glycosuria. Also the addition of 50 gm. of bread on Feb. 7, 8 and 9 resulted in no glycosuria, but on Nov. 10 it gave rise to 1.69 per cent. of sugar in

456 cc. of urine. Similar glycosuria now persisted on the diet of 1 kg. of lung without bread, and twice returned after being stopped by fast-days, so that on Feb. 20 the diet had to be changed to 500 gm. lung and 100 gm. suet, on which glycosuria remained absent. These fluctuations of tolerance are within the limits of ordinary variation in such animals. The apparent rise is explained by a preceding period of aglycosuria, and the subsequent fall is accounted for by the preceding period of 10 days in which glycosuria had been present most of the time.

To control possible differences in absorption, a comparison was made of intravenous glucose tests on Jan. 31, before the partial thyroidectomy, and on Feb. 28. The weight on the former date was 13.5 kg. and on the latter date 12.5 kg., but the dosage was 1 gm. per kg. based on the original normal weight of 19.1 kg. The amount of 19.1 gm. of Merck anhydrous glucose was weighed out and dissolved in water to make a 20 per cent. solution. This quantity was given each hour by the method of interrupted injections used in several of these series of experiments. The dog was catheterized, blood was drawn from a previously exposed jugular vein, and by an exchange of syringes the sugar injection was given through the same needle. Every 20 minutes thereafter the same program was repeated, one-third of the hourly dose of glucose being injected each time. The results are shown in Table V.

TABLE V. *Dog D4-62.*

JAN. 31			FEB. 28			TIME
Plasma Sugar, %	Urine		Plasma Sugar, %	Urine		
	Vol. cc.	Glucose %		Vol., cc.	Glucose, %	
0.100	124	0	0.088	158	0	Before 1st injection
0.196	10	2.94	0.210	20	4.6	" 2nd "
0.385	21	3.23	0.345	31	4.75	" 3rd "
0.385	25	4.35	0.357	34	4.03	" 4th "
	21	5.56	0.384	36	4.14	" 5th "
0.455	28	6.25	0.400	40	4.03	" 6th "
0.455	27	5.41	0.486	38	3.86	" 7th "
						Injecs. discontinued
0.416	33	4.54	0.384	49	6.17	20 min. aft. 7th injec.
0.286	21	3.57	0.212	32	4.60	40 " " " "
0.384	4	2.08	0.185	7	3.47	60 " " " "
0.137	7	trace	0.170	Not Cath eterized		80 " " " "
0.088	10	0	0.149	36	2.08	100 " " " "

TABLE VI. *Dog D4-73.*

DATE 1917	Weight Kg.	URINE				BLOOD				REMARKS
		Vol., cc.	Sugar gm.	Acetone qual.	Total-N gm.	NH ₃ -N gm.	Plasma Sugar mg. per 100 cc.	Plasma CO ₂ vol. %	Corp. vol. %	
Aug. 4	—	806	8.60	Slight-	3.84	0.44	—	—	—	Fed 100 gm. suet.
" 5	—	1164	9.24	mod.	3.60	0.53	—	—	—	" " "
" 6	—	1070	V. Faint	Faint	2.16	0.43	—	—	—	Not fed.
" 7	—	910	neg.	neg.	2.48	0.24	244	63.3	44.3	Fed 100 gm. suet.
" 8	15.8	888	"	"	2.44	0.28	145	68.1	37.5	" 200 gm. lung and 100 gm. suet.
" 9	—	1095	doubtful	Slight-	2.40	0.38	263	—	43.1	Not fed.
" 10	15.6	1125	Faint	Faint	3.60	0.29	151	47.1	48.0	" "
" 11	—	380	neg.	neg.	0.14	0.95	278	51.0	39.8	" "
" 12	—	480	"	"	0.28	3.85	—	—	—	Fed 100 gm. lung and 100 gm. suet. Vomited diet.
" 13	—	795	Faint	Faint-	0.32	3.60	333	—	—	Not fed.
" 14	—	790	"	"	2.56	0.26	384	—	—	Fed 50 gm. suet. Vomited.
" 15	—	558	Faint	neg.	3.66	1.80	—	—	—	Not fed.
" 16	—	435	V. Faint	Faint-	3.75	1.70	357	50.0	—	" "

The tests showed no difference of glucose assimilation before and after removal of one lobe of the thyroid. As the suggestions of clinicians for the modification of human diabetes have pertained to partial, not total thyroidectomy, this test of the influence of partial thyroidectomy was undertaken with this point in view.

Dog D4-73, a brindle female mongrel aged 6 years, weighing 17.25 kg., was partially depancreatized on Jan. 17, 1917. The tissue removed weighed 36.4 gm., and the remnant about the main duct was estimated at 4.8 gm. (1/8-1/9). Glycosuria could at first be produced only by addition of glucose to the diet. After the tolerance was thus reduced, the dog was used for prolonged high fat diets, sometimes with and sometimes without glycosuria, in an unsuccessful attempt to produce acidosis, as will be described elsewhere. At first the body weight was thus raised above 20 kg. Later it fell with progress into severe diabetes. In the latter part of July and early days of August it approximated 15 kg. The dog had reached a dangerously cachectic state, so that no prolonged fasting could be endured, and it was improbable that even the longest fasting could halt the glycosuria. Therefore on Aug. 10 complete thyroidectomy was performed, in order to learn whether any practical benefit could thus be attained in the direction of saving the dog's life. The results are shown in Table VI.

One large parathyroid was left on each side with its blood supply intact. Both thyroid lobes were dissected out completely with the exception of tiny shreds adhering to the parathyroids or their vessels. No symptoms of tetany or other disturbances followed the operation. The diet consisted chiefly of suet both before and after the operation, in order to supply a maximum of nutrition in the form of fat together with a minimum of sugar-forming material. It was eaten and digested well up to Aug. 14. The dog then became too weak to eat, and died in the usual cachexia on Aug. 16. The thyroidectomy may have hastened death by a day or two, but had no other evident effect. The decline of glycosuria and hyperglycemia was no greater than is known to occur in the terminal cachexia of many severely diabetic animals.

The gross autopsy was normal. The two parathyroids appeared normal, and microscopically were found accompanied

by a few large thyroid vesicles, full of colloid. The pancreas remnant, normal in appearance and consistency, weighed 5.2 gm. Microscopically it showed very slight fibrosis, not involving the islands. The islands were on the point of disappearing through hydropic degeneration, being scarce, small, and composed of maximally vacuolated cells. The practical absence of functional island tissue made evident the futility of attempting to aid such an animal by thyroidectomy.

Dog E5-97, a brown male bulldog mongrel aged 6 years and weighing 17.5 kg., was partially depancreatized on Sept. 28, 1917. The tissue removed weighed 44.0 gm., and the remnant about the main duct was estimated at 4.7 gm. (1/10-1/11). Tests then showed the susceptibility to prompt and heavy glycosuria on either bread or meat feeding, but the diabetes was kept under control by fasting and very low protein-fat diets.

Nov. 1, when the body weight had been reduced to 13.5 kg., an intravenous glucose tolerance test was performed. Feeding tests during the following days showed that the undernutrition had raised the dog's tolerance to such a point that as much as 1 kg. of beef lung and 100 gm. of suet could be eaten without glycosuria. A standard diet of 600 gm. lung and 100 gm. suet caused no hyperglycemia when taken for a week. The addition of 50 gm. bread for 1 day caused no glycosuria, but an increase to 100 gm. of bread resulted in slight glycosuria the first day and heavy glycosuria (2.9 per cent. in 1040 cc. urine) the second day.

Nov. 21, with normal urine and blood on the standard diet, and with body weight of 13.7 kg., the thyroid was removed as completely as possible without damaging one large parathyroid which was left on each side. Slight glycosuria occurred during a few hours after operation, but on the following days the standard diet was taken without apparent abnormalities of any kind.

Nov. 28, the standard diet of 600 gm. lung and 100 gm. suet was increased by 50 gm. bread. Nov. 29, the bread was increased to 100 gm., still without glycosuria. Nov. 30, an increase to 150 gm. bread caused an excretion of 2.7 per cent. glucose in 350 cc. urine. Glycosuria then remained absent on the standard diet. Beginning Dec. 8, 100 gm. bread was again added daily, with the result of slight glycosuria for 2 days

and absence of glycosuria for the ensuing 3 days. Dec. 13, a little milk was given in addition to the lung-suet-bread diet, still without glycosuria. The standard lung-suet diet was then resumed.

Dec. 20, when the body weight was 13.6 kg. and the general health apparently good, another intravenous tolerance test was performed. The same test was repeated on April 21, when the weight was 13.0 kg. Blood sugar analyses on other days will be mentioned below.

Jan. 15, 1918, the body weight was 13.0 kg., and the daily addition of 5 gm. of thyroid powder (Armour's) to the standard diet was commenced. By Jan. 28 the body weight had fallen to 12.25 kg. and the dog seemed distinctly weaker. The rectal temperature was not above 38.8°C. The heart rate at rest was ordinarily only 120 to 130, but the rhythm was more irregular than observed in normal dogs, and slight exertion caused undue acceleration of the rate. Beginning Feb. 5, the standard diet was continued without thyroid. By Feb. 20 the body weight had risen to 12.9 kg. and the general condition appeared better.

Beginning Feb. 21, the diet was increased to 1200 gm. lung and 100 gm. suet, except on days when the standard diet was resumed for blood sugar analyses. The feces had gradually been growing more bulky for some time past, and though the dog ate the increased diet eagerly, digestion and absorption continued to fail, so that by April 17 the weight was still only 13 kg. From April 18 to 21 inclusive, the diet of 1200 gm. lung and 100 gm. suet was increased by the addition of 100 gm. bread. Glycosuria was absent until the last day, when there was 0.95 per cent. glucose in 550 cc. urine. Bread was then omitted and the glycosuria ceased.

The feces continued to grow more bulky and foul, until they obviously contained most of the protein and fat of the diet. By May 18 the weight had fallen to 9.3 kg., and the dog was moribund from weakness. Intelligence and courage were preserved; there was no physical or psychic change suggestive of myxedema. The penis hung protruded from the prepuce, and the exposed portion of it was black with dry gangrene. The rectal temperature was below 33°C. The pulse was 69 per minute and very feeble. The respiration was only 8 per minute, but was dyspneic. Inspiration was prolonged until the chest

was distended to its utmost capacity; expiration was protracted and forcible, squeezing out all possible air by a maximum effort of contraction. There were no pauses between respiratory movements. The urine remained free from sugar and acetone. The blood findings were as follows: corpuscle volume, 35.5 per cent.; plasma sugar 0.27 per cent.; plasma acetone negative (nitroprusside qualitative and Van Slyke quantitative); CO_2 capacity of plasma 32.8 volume per cent. All these figures, obtained in the forenoon, were practically duplicated in the blood taken at autopsy in the evening. The reason for the high level of plasma sugar is unknown. The low bicarbonate concentration, with other tests for acidosis negative, is perhaps explained by dyspnea according to the work of Yandell Henderson.

The autopsy obtained at 9 p.m. was grossly negative except for extreme emaciation. The remains of thyroid-parathyroid tissue obtained on the two sides weighed 0.2 gm. in total. The pancreas remnant, normal in appearance and consistency, weighed 3.7 gm. The reduction as compared with the 4.7 gm. estimated at the original operation may be sufficiently explained by the wasting of all organs in cachexia. Microscopically normal parathyroids were found, with only a trifle of thyroid tissue adjoining them. This latter tissue seemed to consist of interlacing cords of cells, with only occasional small vesicles containing a trifle of colloid. The pancreatic tissue was normal except for a slightly foamy appearance of the cytoplasm of both island and acinar cells, probably connected with the cachexia. The islands otherwise were normal in number, architecture and cytology, and hydropic degeneration was absent. The other viscera showed no more than simple atrophic changes.

The influence of thyroidectomy upon the carbohydrate assimilation was judged by two criteria, namely by intravenous glucose tests and by the hyperglycemia following a protein-fat diet. The glucose tests are shown in table VII.

The intravenous tolerance tests were used to exclude irregularities of intestinal absorption. The method employed was that of discontinuous injections, as described in several previous papers. An external jugular vein of the fasting animal was painlessly exposed about an hour before the beginning of the experiment. A solution containing 20 per cent.

TABLE VII. Dog E5-97. Intravenous Glucose Tests.

TIME	PLASMA SUGAR mg. per 100 cc.				URINE						REMARKS
	Nov. 1	Dec. 20	April 21		Nov. 1		Dec. 20		April 21		
					Vol. cc.	Sugar gm.	Vol. cc.	Sugar gm.	Vol. cc.	Sugar gm.	
4:05pm	95	172	146		70	neg.	78	neg.	30	neg.	Blood drawn before injec.
4:25pm											Given 1st. injection
4:40pm											" 2nd. "
4:55pm											" 3rd. "
5:10pm											" 4th. "
5:20pm	286	455	370			no urine	92	0.38	90	3.47	" 5th. "
5:25pm											" 6th. "
5:40pm											" 7th. "
5:55pm											" 8th. "
6:10pm	294	370	400		70	1.71	22	0.87	60	2.73	15 min. after last injection
6:25pm	164	286	228		no urine		no urine		40	1.25	" "
7:25pm		149	137		40	0.59	17	neg.	32	0.27	" "
8:25pm	145										140 " "

by weight of Merck's anhydrous glucose was prepared. The dosage was arbitrarily chosen as 1 gm. per kg. per hour on the basis of 14 kg. body weight. In beginning the experiment, the dog was catheterized, a blood sample was drawn from the exposed jugular with a syringe, and an injection of one-fourth of the hourly dose (3.5 gm. glucose, or 17.5 cc. of solution) was given with a different syringe through the same needle. Further injections were given at the end of 15, 30 and 45 minutes; but instead of taking blood and urine samples each 15 minutes, as usual, these were taken only hourly, for the two hours during which injections were given, and for the following two hours.

Three identical tests were performed, namely on Nov. 1 before thyroidectomy, on Dec. 20 early in the period after thyroidectomy, and on April 21 late in the period after thyroidectomy. The two latter tests indicated a distinct fall of tolerance as compared with the first test, judged especially by the curve of hyperglycemia. The excretion of glucose was slightly less on Dec. 20 than on Nov. 1, but on April 21 was much higher. The apparent lowering of assimilation may have been due to cachexia or any other accidental cause, but it must at least be concluded that the tolerance according to the intravenous tests was not raised by thyroidectomy.

The second criterion of assimilation adopted was the influence of a standard mixed meal, consisting of 600 gm. lung, 100 gm. suet, and 50 gm. bread. On selected days this was substituted for the regular diet, and analyses of blood and urine were obtained before feeding and 3 and 6 hours after. No glycosuria occurred on any occasion, but on the whole the plasma sugar curve was lower in the various tests after thyroidectomy than it had been on Nov. 14, before thyroidectomy. It will be seen in table VIII. that the plasma sugar

TABLE VIII. *Dog E5-97. Feeding Tests.*
Plasma sugar, mg. per 100 cc.

	Nov. 14	Dec. 27	Jan. 15	Jan. 28	Feb. 4	Feb. 11	Mar. 7	Apr. 17
Before feeding....	126	151	133	143	167	152	128	125
3 hrs. after feeding	183	161	119	103	149	182	132	116
6 " " "	174	161	149	161	161	—	115	119

held its lowest values on March 7 and April 17, after cachexia had become marked. The results of the intravenous tests indicated that the dog's ability to take higher diets of carbohydrate and protein with less tendency to hyperglycemia or glycosuria was not due to a true increase of tolerance. On the other hand the character of the feces and the stationary or falling weight with increased diets served to explain the lower sugar curves after feeding as due to impaired absorption. This finding is not contrary to the observation of Janney and Isaacson that absorption is not impaired with thyroid deficiency, for in the present instance thyroid and pancreatic deficiency coexisted and the results suggested that the combination was more serious in all respects than the deficiency of only one organ.

The feeding of 5 gm. powdered thyroid daily from Jan. 15 to Feb. 4 did not restore any better health. There were some indications that this quantity represented a toxic excess of thyroid, but the important feature is that such a quantity failed to cause glycosuria at any time or any special hyperglycemia in the feeding test of Feb. 4 (table VIII), though the dog was actually diabetic. This observation therefore agrees with the experiments described above concerning the negative effects of thyroid excess in depressing pancreatic function.

In conclusion, it may be specially noted that the loss of nearly the whole thyroid is generally well borne by dogs, and pancreatectomy to the degree used in this experiment is compatible with indefinite longevity and liveliness at the price of some limitations of diet and body weight. The combination of the two deficiencies, however, seemed to produce a fatal cachexia. The results of animal experiments should therefore be studied very carefully before venturing upon an attempt to balance an existing pancreatic deficiency by a reduction of thyroid tissue in human patients.

Dog D4-45, a yellow male mongrel aged 1 year, weighing 18.4 kg. in a state of medium nutrition, was partially depancreatized on Nov. 13, 1916. The tissue removed weighed 31.2 gm. The remnant about the main duct was estimated at 2.1 gm. (1/15). Fasting until Nov. 20 was then necessary to check glycosuria. A diet of lean beef and suet was next built up very gradually. At first 100 gm. meat sufficed to cause gly-

cosuria, requiring fasting to stop it. By Dec. 29 the body weight had been reduced to 13 kg., and the limit of food tolerance had been fixed at 300 gm. meat and 100 gm. suet. Repeated attempts to feed 400 gm. meat resulted in marked glycosuria. Though thin, the dog was strong and lively, and was highly intelligent and affectionate.

On Dec. 29, all thyroid tissue was removed, with the exception of such tiny shreds as were necessary to assure the survival of one large parathyroid on each side. No glycosuria or tetanic symptoms resulted. The dog fasted on the day of operation and afterward was fed almost entirely on suet up to Jan. 8., merely for the incidental purpose of observing whether the double thyroid and pancreatic deficiency created any special susceptibility to acidosis. Acetone remained absent or trivial in amount, as in a normal dog.

As the dog was not catheterized, the volume of urine and its content of total nitrogen and ammonia nitrogen were subject to irregular variations. The urine was generally scanty and concentrated, but no more so than before operation. Seemingly because of the high fat diet mentioned, the ratio of ammonia to total nitrogen was high during the first few days shown in the table, but later was normal. The principal observations pertain to the influence of thyroidectomy upon the diabetes or the food tolerance, as summarized in table IX.

The 4 days, Dec. 9 to 12, constituted a fasting period for control purposes, as mentioned below.

Following thyroidectomy, it was possible from Jan. 8 to 13 to raise the diet not only to 400 but even to 500 gm. of lean meat without glycosuria, thus decidedly surpassing the former tolerance. The increase to 600 gm. on Jan. 14 gave rise to glycosuria of 10.6 gm., which was controlled by fasting. No marked hyperglycemia was found in the blood taken mornings before feeding during the above period. Jan. 17 to 23, 400 gm. meat with 100 or 200 gm. suet was tolerated daily. After successive increases, from Jan. 27 to 29 as much as 800 gm. meat and 200 gm. suet was eaten daily without glycosuria. The plasma sugar in the morning before feeding remained low as before.

Jan. 30 to Feb. 2 was a 4-day fasting period, for comparison with the control period of Dec. 9 to 12 before thyroidectomy. The dog was catheterized at the beginning of the first day and

TABLE IX. *Dog D4-45.*

DATE 1917- 1918	Weight Kg.	URINE				Plasma Sugar mg. per 100 c.	REMARKS
		Vol. cc.	Sugar gm.	Acetone Qual.	Total-N gm.		
Dec. 9		502	5.82	neg.	9.43	0.65	Not fed.
" 10		164	Faint	"	6.74	0.46	"
" 11		256	neg.	"	5.04	0.44	"
" 12	13.6	147	"	"	4.01	0.35	"
Jan. 8	12.6	148	"	"	2.29	0.99	"
" 9		438	"	slight	3.46	1.58	Fed 100 gm. meat and 200 gm. suet.
" 10	12.3	378	"	"	3.45	1.66	" 200 "
" 11	12.3	508	"	faint	7.57	2.24	" 300 "
" 12	12.0	228	"	neg.	4.36	1.79	" 400 "
" 13	12.1	262	"	"	5.71	1.99	" 500 "
" 14		402	10.57	faint	8.68	1.69	" 600 "
" 15	12.1	90	faint	neg.	2.23	0.69	Not fed.
" 16	11.9	118	V. faint	"	2.14	0.87	Fed 200 gm. suet.
" 17	12.0	278	neg.	"	6.19	1.67	Fed 400 gm. meat and 100 gm. suet.
" 18	11.9	148	"	"	—	—	" " "
" 19		201	"	"	6.85	0.46	" " "
" 20	12.0	203	"	"	6.27	1.12	" " "
" 21		160	"	"	6.13	0.23	" " "
" 22	12.2	198	"	"	7.52	0.46	" " "
" 23	12.2	182	"	"	7.43	0.33	" " "
" 24	12.5	214	"	"	8.84	0.62	" " "
" 25	12.7	324	"	"	13.71	0.78	" " "
" 26	12.8		Urine lost	"			500 "
" 27	12.7	322	neg.	"	10.48	0.30	600 "
" 28		360	"	"	10.60	0.33	700 "
" 29		408	"	"	13.41	0.77	800 "
" 30	12.7	302	"	"	8.61	0.73	" " "
" 31	12.1	105	"	"	3.02	0.89	Not fed.
Feb. 1	12.0	110	"	"	2.97	0.39	" " "
" 2	11.9	70	"	"	1.85	0.06	" " "

"	3	11.4	238	"	9.86	0.27	95	Fed 500 gm. meat.	
"	4	12.2	228	"	9.30	0.37	—	" 800 "	
"	5	11.7	378	1.50	16.15	0.80	120	" 1000 "	
"	6	11.7	262	neg.	9.25	0.46	145	" 500 "	and 100 gm. suet.
"	7	11.4	222	"	8.68	0.38	—	" " "	" " "
"	8	11.5	282	"	10.42	0.69	—	" " "	" " "
"	9	12.2	282	"	11.09	0.69	116	" " "	" " "
"	10	12.0	242	"	8.93	0.81	—	" " "	" " "
"	11	12.1	282	"	12.00	0.44	—	" " "	" " "
"	12	12.1	188	"	8.69	0.40	—	" " "	" " "
"	13	11.9	240	"	8.92	0.55	118	" " "	" " "
"	14	11.7	258	"	8.92	0.68	98	" " "	" " "
"	15	11.7	392	"	13.26	—	—	" " "	" " "
"	16	11.7	372	"	14.21	—	—	" " "	" " "
"	17	11.7	235	"	9.65	—	—	Fed same diet with 12 grains thyroid.	
"	18	11.7	196	"	9.33	—	—	" " "	same thyroid.
"	19	11.8	218	"	8.50	—	—	" " "	20 grains thyroid.
"	20	11.6	546	"	15.36	—	—	" " "	32 " "
"	21	11.8	330	"	13.79	—	—	" " "	48 " "
"	22	11.3	210	"	10.05	—	—	" " "	72 " "
"	23	11.3	278	"	10.90	—	—	" " "	96 " "
"	24	11.3	460	"	20.10	—	132	" " "	" " "
"	25	11.3	288	4.75	12.15	—	178	" " "	Thyroid stopped.
"	26	11.5	750	neg.	11.08	—	—	" " "	" " "
"	27	11.5	356	"	13.70	—	118	" " "	" " "
"	28	11.5	212	"	9.10	—	—	" " "	" " "
Mar. 1	1	—	238	"	9.30	—	—	" " "	" " "
"	2	—	350	"	14.10	—	—	" " "	" " "
"	3	11.8	250	"	7.60	—	—	" " "	" " "
"	4	—	260	"	11.85	—	—	" " "	" " "
"	5	11.5	328	"	14.65	—	—	" " "	and 25 gm. bread.
"	6	11.4	340	"	11.60	—	—	" " "	" 50 " "
"	7	11.6	340	"	9.15	—	—	" " "	" " "
"	8	11.6	428	9.75	14.50	—	—	" " "	Bread stopped.
"	9	11.4	396	neg.	10.55	—	123	" " "	" " "

the end of the last day. The nitrogen output fell more rapidly and reached a lower level than in the normal state, thus showing the change of nitrogen metabolism which is known to be characteristic of total thyroidectomy.

Beginning with 500 gm. meat on Feb. 3, the diet by Feb. 5 was increased to 1 kg. of meat, which caused glycosuria of 1.5 gm., together with hyperglycemia of 0.145 per cent. on the following morning. The urine and blood then remained normal on a diet of 500 gm. meat and 100 gm. suet continued to Feb. 15.

Feb. 16 to 24, the same diet was continued with addition of thyroid tablets, beginning with dosage of 12 grains and increasing to 96 grains daily. The blood sugar rose, and glycosuria of 4.75 gm. was present on Feb. 24. This glycosuria ceased immediately with no other change than omission of the thyroid feeding. On the second day also the plasma sugar had fallen to normal. For closer comparison of the periods before and during thyroid administration, the plasma sugar was followed at 2-hourly intervals on representative days after feeding the identical diet.

On Feb. 14, before thyroid treatment, the fasting plasma sugar was 0.098 per cent. The diet of 500 gm. meat and 100 gm. suet was then fed, and the plasma sugar at 2-hourly intervals thereafter was 0.125, 0.118, 0.141, 0.151, 0.163, and 0.169 per cent.

On Feb. 23, during the period of highest thyroid dosage, the morning plasma sugar was 0.132 per cent. After the same diet, the plasma sugar at 2-hour intervals was 0.172, 0.172, 0.196, 0.238, 0.263, and 0.303 per cent. The unusually slow rise of the sugar curve is presumably explained by delayed food absorption. As this delay, however, was similar on the two days but the elevation was so much greater after thyroid feeding, it may be inferred that the thyroid had an actual influence upon the assimilative power.

After discontinuance of thyroid treatment, the diet of 500 gm. meat and 100 gm. suet continued to be tolerated. Beginning March 5, additions of first 25 and then 50 gm. of bread were borne without glycosuria, but the second day with 50 gm. of bread resulted in the excretion of 9.75 gm. of sugar. The former protein-fat diet was then resumed.

The dog had gradually lost weight notwithstanding the

liberal diets, and the feces, though always well formed, had become increasingly bulky and fatty, with a strong odor of fatty acids. At the same time a change resembling myxedema or cretinism occurred. The skin became thickened, and most of the hair was lost. The animal became sluggish, stupid almost to the point of idiocy, and indifferent to everything except a greedy desire for food. No reason is known why this change should have been produced in this dog and not in any of the others used, unless it may be the fact that this dog was much younger than the others and still retained somewhat of a puppy appearance at the time of beginning the experiment.

March 22, the dog was found weak and cold, barely able to stand, weighing only 8.8 kg. The urine had remained negative for sugar and acetone. Blood taken from a jugular vein showed corpuscle volume (hematocrit) of 30 per cent., plasma sugar 0.038 per cent., plasma bicarbonate (Van Slyke) 40.4 volume per cent., acetone absent.

After chloroforming, the gross autopsy was negative except for emaciation. The liver weighed only 271 gm., the kidneys together 67.5 gm., the spleen 8.5 gm. The pancreas remnant, normally soft and lobulated, weighed 2.8 gm. In view of the general atrophy, this weight as compared with the estimate of 2.1 gm. at operation may be taken to represent an appreciable hypertrophy of the remnant. The remains of thyroid-parathyroid tissue on each side of the neck were not much larger than a normal parathyroid.

Microscopically, the principal viscera were normal except for atrophy. The cortex of the adrenals was normal; the medulla was normal except for vacuolation in many of the cells, a change probably associated with the extreme cachexia. The parathyroids appeared normal. The thyroid tissue accompanying them was of microscopic dimensions, and consisted chiefly of networks of cells, with very few typical vesicles and very little colloid. The pancreas remnant was free from fibrosis. The acini were normal and well filled with zymogen. Islands were normal in number, size and structure, except for a foamy vacuolation of the cytoplasm, not resembling hydropic degeneration and probably attributable to the cachexia.

Three possible criticisms of such experiments may be answered as follows:

First, the cachexia is not due to deficiencies of diet. Bone meal was given regularly to supply salts and prevent diarrhea. Normal or potentially diabetic dogs are able to thrive indefinitely on such diets.

Second, the purpose of superposing a thyroid deficiency upon a pancreatic deficiency seems to have been strictly accomplished. Parathyroid deficiency need not be considered as a factor, for as far as known two parathyroids suffice for the bodily needs, and tetany and other recognizable signs of parathyroid deficiency were absent. Also, regeneration of thyroid tissue was so slight as not to interfere with the experiments; the extreme regeneration reported by some authors was not observed.

Third, the experiment on dog D4-45 was planned to include fecal analyses for direct proof of impaired food absorption. The feces for the different periods were demarcated with carmine, saved and dried for the purpose, but circumstances prevented the analyses, as also most of the studies of lipemia which were contemplated in this animal. The gross character of the feces, together with the dog's progressive emaciation, gave sufficient indirect evidence of the impairment of absorption. Two other dogs, one normal and the other partially depancreatized, were used as controls on the identical diets with dog D4-45, and their feces also were saved but not analyzed. As they thrived and had less bulky feces, the impaired absorption and cachexia of dog D4-45 may properly be attributed to the thyroidectomy. These troubles, however, in dog D4-45 were in no way relieved by the thyroid feeding, and likewise the appearances of myxedema and the stupid behavior remained unaltered during this time.

It must be concluded that there was a slight thyroid influence upon the assimilation in this diabetic animal. The food tolerance may have been a trifle higher after than before thyroidectomy; in particular, thyroid dosage seemed to induce hyperglycemia and glycosuria in a manner not explainable by a difference in food absorption. On the other hand, the animal still remained diabetic, and the apparent slight rise of tolerance was too dearly purchased at the price of a fatal cachexia. This evident injury robs the procedure of any practical therapeutic possibilities. From the theoretical standpoint, the partial suppression of the usual diabetic symp-

toms by an added injury of this character by no means indicates that the thyroid is antagonistic to the pancreas or plays any specific rôle in diabetes.

REMARKS.

1. *Concerning production of diabetes by thyroid excess.*— Though some experiments were negative, several positive results support the conclusion that thyroid feeding may be responsible for hyperglycemia and glycosuria in dogs which are already diabetic. The feeble influence of extremely large thyroid doses is perhaps explainable by destruction or poor absorption of the thyroid hormone in the dog's intestine. For this reason it is desirable that the experiments should be repeated by means of parenteral injections of Kendall's thyroxin, which may be expected to exert a more powerful action. In the interpretation of any such results, a careful distinction should be maintained between the causation of hyperglycemia or glycosuria and the causation of diabetes. A combination of experimental and clinical evidence seems to demonstrate that the intoxication or the elevated metabolism of thyroid excess may aggravate existing diabetes and increase the tendency to hyperglycemia, glycosuria and downward progress. The question whether simple hyperthyroidism may give rise to hyperglycemia or impairment of glucose utilization in a normal organism without pancreatic or other disturbances may be considered still doubtful.

None of these decisions concerning either the diabetic or the normal organism have any bearing whatever upon the question of the causation of diabetes by thyroid excess. The analogous situation regarding carbohydrate excess deserves emphasis. There is no doubt that sugar and starch can produce glycosuria and downward progress in diabetes; also, sufficient quantities of sugar can produce hyperglycemia and glycosuria in the normal organism; furthermore, carbohydrate is far more powerful in these respects than the thyroid has ever been shown to be. Nevertheless, the fact is recognized both experimentally and clinically that no degree of carbohydrate excess can actually cause diabetes. Attention was formerly called⁵⁶ to the demonstration that animals with just the right degree of partial pancreatectomy may be subjected to the most extreme excesses of starch and sugar for months continuously

without the slightest increase of diabetic tendency, and then diabetes may result from the removal of five-tenths, two-tenths, or even one-tenth of a gram of additional pancreatic tissue. When maximal carbohydrate excess is unable to overcome the influence of one-tenth of a gram of normal pancreatic tissue (only a small part of which consists of islands), the conclusion is unavoidable that such excess can serve only to intensify an existing or latent diabetes and is powerless as a primary factor in the causation of diabetes. The same rule must be applied to the seemingly feebler influence of the thyroid hormone. There has never been the least evidence that thyroid excess can serve in any degree to cause diabetes. The experiments with animals depancreatized almost to the point of diabetes are simple to perform. The only positive proof must consist in the production of true diabetes in an animal which was formerly not quite diabetic. If the largest thyroid dosage proves unable to neutralize the activity of the smallest fraction of a gram of pancreatic tissue, the numerous loose claims concerning a thyroid factor in the etiology of diabetes should be silenced. From the slightness of its demonstrated influence upon carbohydrate metabolism, the writer is inclined to predict a negative conclusion of such experiments upon the rôle of the thyroid in the causation of diabetes.

2. *Concerning suppression of diabetes by thyroid deficiency.* — The results with thyroidectomy agree with previous views that thyroid deficiency may sometimes reduce or abolish the glycosuria and hyperglycemia of diabetes. No one, however, has ever furnished the slightest evidence that reduction of sugar by this means is beneficial. It is an unphysiological form of reasoning to argue that two deficiencies may interact so as to restore normal metabolism. These experiments accomplished the purpose aimed at by surgeons who have sought to relieve diabetes by reduction of thyroid tissue, and they proved that one deficiency is merely added to the other so as to increase the injury to health and life. Thyroidectomized dogs are known to live for long periods in fair physical condition. Those with the degree of diabetes represented in dog D4-45 can live for a long or unlimited time on regulated diets which maintain a satisfactory state of nutrition. But with thyroidectomy superimposed upon diabetes, the result was a fatal cachexia which could not be halted either by thyroid feeding

or by diet. It has long been known, and was further shown in paper 4 of this series, that any serious cachexia may abolish diabetic hyperglycemia and glycosuria. No specific action, therefore, need be assumed in the cachexia resulting from thyroidectomy. When the diabetes is sufficiently severe thyroidectomy does not abolish glycosuria.

It seems necessary to reiterate the principle that diabetes is deficiency of the internal secretion of the pancreas; it is not synonymous with glycosuria or any other symptom, and reduction of glucosuria, nitrogen excretion or any other symptoms by thyroidectomy or other mutilations does not demonstrate a reduction of the severity of the diabetes or an antagonism between the pancreas and other glands. To prove that the thyroid hormone either inhibits the function of the islands of Langerhans, or opposes the action of their internal secretion upon the bodily metabolism, it should be shown that mildly diabetic animals with an accurately determined food tolerance may be benefited by some degree of thyroid reduction, which will enable their small pancreas remnant to function more effectively. As stated, these experiments have failed to reveal such a specific relationship, and removal of thyroid tissue has not influenced diabetes unless carried to the point of a fatal cachexia. As the animal experiments are simple to perform, and as they have thus yielded either negative or injurious results, operations upon the normal thyroids of human diabetics must be considered unjustifiable.

CONCLUSIONS.

1. Thyroid excess may aggravate the symptoms of an existing diabetes, but has never been demonstrated as contributing to the actual causation of diabetes.
2. Thyroid deficiency may partially or wholly suppress diabetic glycosuria and hyperglycemia, but this effect is rationally explained as the result of injury or cachexia. There is no indication that the intrinsic severity of the diabetes is lessened or that one deficiency can neutralize another.
3. Neither the excess nor the deficiency experiments can properly be interpreted in favor of an antagonism between the pancreas and the thyroid or of a thyroid element in diabetes.

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CLINICAL OBSERVATIONS CONCERNING PROGRESSIVENESS OF DIABETES.

By JAMES W. SHERRILL, M. D.

From the Physiiatric Institute, Morristown, N. J.

In the paper of Alien and Sherrill¹ and other publications, attention has been called to the instructive possibilities of prolonged observations of suitable diabetic cases under thorough dietetic control. The following studies of five cases are presented as a contribution to the question whether diabetes is an inherently and inevitably progressive disease, or whether its progressiveness is determined entirely or chiefly by overload of the weakened pancreatic function. These cases are examples of severe diabetes in youthful patients, which were demonstrably progressive up to the time of beginning strict treatment, and have since been under close and accurate observation for a sufficient period to afford some basis of judgment of their lack of progressiveness under treatment.

Two sources of error must be guarded against in such an investigation. One consists in mistakes and deceptions on the part of patients. To emphasize the need of close control, mention need only be made of the former publications from some of the best known European clinics, announcing D:N ratios far above 3.6:1, even in patients under institutional care. For this reason, downward progress in patients supposedly following diet at home is particularly inconclusive as evidence of an inherent and inevitable progressiveness of diabetes. A second possible error may be found in the blood sugar analyses. The method of Benedict² was used in this work. Occasional experiences have suggested that the method of Folin and Wu, however admirable and exact in sufficiently skilled hands, is actually used in such a manner as to give unduly low results in many clinical laboratories. Low figures are comforting to both physicians and patients, and encourage high diets. But inasmuch as over-strain of the pancreatic function to the extent of moderate hyperglycemia suffices to cause downward progress in the severest diabetic cases, it is essential

for correct conclusions that the analyses shall be thoroughly reliable, or, if there are to be any errors, that the readings shall be too high rather than too low.

Case No. 85. — Male; American; age 30; single; physician.

Family history: No diabetes has been known in the family. The patient's father died at 30 of typhoid fever. His mother is healthy at 60 years of age. One brother, living and well, is slightly obese.

Past history: The past history has been negative except for measles, whooping cough, and numerous attacks of bilateral otitis media in childhood. The habits have been regular and healthful, without alcoholic indulgence or excess in food. With a height of 5 feet 10 inches, the average weight has been 155 to 165 pounds, the maximum 178 pounds at the age of 21.

Present illness: About April 1, 1915 the patient, as a medical student, had a urinalysis, which was normal. During April he suffered a severe bilateral otitis media with much pain for twenty-four hours, relieved by rupture of the ear drums. May 1, when apparently entirely well, he experienced an acute onset of polyphagia, polydipsia and polyuria. He ignored these symptoms until one month later his vision became impaired so that he was unable to recognize persons or objects across a room. He also had considerable air hunger, but no nausea or vomiting. The first diagnosis was made June 16, six week after the onset, when a physician whom he then consulted discovered 5 per cent. glycosuria and heavy nitroprusside and ferric chloride reactions in the urine. During this time the weight had diminished from 175 to 165 pounds. Restriction of starch and sugar for 24 hours reduced the glycosuria to 1.5 per cent., and one day of fasting then stopped it entirely. Until September, 1916, he was free from glycosuria, except occasional traces, on a diet of unlimited quantities of protein, fat, and 5 per cent. vegetables. The weight fell to 155 pounds. Acidosis and other symptoms remained absent, and he completed his second year in medical school. Occasional blood analyses were performed but the treatment was guided essentially by the urine tests, the diet being continued until a trace of glycosuria appeared, and a single fast day being then used to stop it.

From September 1, 1916 to September 1, 1917 the patient followed a more rigid, accurately weighed diet, averaging 60 to 70 gm. protein, 20 to 30 gm. carbohydrate, and 1000 to 1200 calories, with weekly partial fast days on approximately one-half the regular diet. Urine tests were made daily. Glycosuria occurred only five times during the entire year, and only for a few hours on each occasion. The body weight continued to fall on the low diet to 145 pounds. Toward the close of the year, the tendency to glycosuria became greater, and the lowering of tolerance was further aggravated by several attacks of pharyngitis and laryngitis. He completed his third year in medicine, although weakness was becoming troublesome.

From September, 1917, to July, 1918, the accurately weighed diet

averaged 60 gm. protein, 20 gm. carbohydrate, and less than 1000 calories daily. The weight fell to 125 pounds. The basis of treatment was the same as before. Though a few blood sugar analyses were performed and were sometimes normal, the diet was guided by the urine tests. Traces of glycosuria became increasingly frequent, even on the lower diet. Toward the close of this period, fasting on only 30 gm. protein for four or five days continuously was necessary to bring the blood sugar to normal. Bed rest was necessary on a number of days. He nevertheless succeeded in graduating from medical school in June, 1918.

Following his graduation, he returned to his home, where he managed his own diet for a period of one and a half years. He was unable to do light forms of manual labor during the first year, but could walk two or three miles daily, and attempted to carry on a little medical practice. From June, 1918, to March, 1919, his diet consisted of 60 gm. protein, 2 to 20 gm. carbohydrate, and 600 calories. At no time did the diet exceed 700 calories. The blood sugars, which were analyzed by the patient himself, ranged from 120 to 275 mg. per 100 cc. It was necessary to restrict the diet closely at times in order to prevent glycosuria. Glycosuria occurred six times, and was cleared only with difficulty. It was necessary to reduce the diet to 300 calories to render the urine sugar-free, and a week or ten days of 300 calories was necessary to reduce the blood sugar to normal. At no time since the onset of the disease did he abandon diet or become lax. He was always careful in regard to details, and weighed his food scrupulously.

In March, 1919, he developed a severe cold. Sugar appeared in the urine and persisted for one week. At the first appearance of glycosuria, he took a weighed diet of 60 gm. protein and 3 gm. carbohydrate, without added fat, and remained on this for three days, but was forced to reduce it to 30 gm. protein and 3 gm. carbohydrate because the sugar did not cease. Four days later the urine became free from sugar. He then remained on 30 gm. protein and 3 gm. carbohydrate for one week. Thereafter the diet was increased gradually to 60 gm. protein, 3 gm. carbohydrate, and 600 calories.

On April 1, 1920 he decided to stay in bed until noon each day, as his strength had gradually decreased to such an extent that slight activity caused prostration. He continued his medical practice for three months, gradually gaining strength. During this time his diet was gradually built up to 60 gm. protein, 15 gm. carbohydrate, and 600 calories without glycosuria. Days of one-half diet were taken each week.

From July, 1919 to November 5, 1919 his diet averaged 60 gm. protein, 5 gm. carbohydrate, and 600 calories, with one day of one-half this amount each week. He found it difficult to remain free from glycosuria, which appeared six to eight times during this interval. A fast day of 30 gm. protein and 3 gm. carbohydrate rendered him free of sugar. On October 15 he had a sudden severe attack of nephrolithiasis, which lasted twelve hours. Typical symptoms were present, accompanied by hematuria and pain. Glycosuria of moderate degree occurred, but was abolished by cutting the diet to 30 gm. protein for two days. From August, 1919 to November 5, 1919 his weight ranged from

120 to 125 pounds, fluctuations being due to water retention and slight edema. He was admitted to the Psychiatric Institute November 5, 1919.

Physical examination: The physical examination was negative, except for marked emaciation. The blood pressure was 127/86. The urine was free from albumin and formed elements. Renal function tests have remained normal, and there have been no further attacks of lithiasis. The patient's record in the Institute is shown in table I.

The patient being admitted with hyperglycemia without glycosuria, treatment was begun with a single fast day, followed by diets low in protein and calories. The attempt to force the diet too rapidly up as high as 60 gm. protein, 15 gm. carbohydrate, and 1400 calories brought a return of hyperglycemia on December 19. This was insufficiently checked by reductions of diet, so that by January 10 the plasma sugar reached 0.429 per cent., and there was moderate glycosuria. Two days of fasting restored a normal blood sugar, and the diet was then built up more cautiously to 1000 calories. This also was in excess of the tolerance, and further undernutrition was necessary in February and March. In the following months up to September, the diets averaged very low because of the frequent recurrences of hyperglycemia. By October and November the weight had been reduced to approximately 100 pounds, and the tolerance accordingly had risen so that diets of 50 gm. protein, 3 gm. carbohydrate, and 700 to 900 calories were tolerated with normal plasma sugar. In the following months, up to the summer of 1920, it became possible gradually to raise the diet as high as 55 gm. protein, 10 gm. carbohydrate, and 1100 calories. The increase of weight to a maximum of 123 pounds in July was due to edema, and the fall to 96 pounds by the end of October was produced by salt-free diet. From October 18 to December 27 the patient was subjected to high caloric diets, first with fat and then with alcohol. As already described by Leclercq³, marked hyperglycemia resulted in both instances. After an undernutrition period up to January 8, 1922 to correct the injury of the overnutrition, the diet of 50 gm. protein, 5 gm. carbohydrate, and 1100 calories was resumed, and the normal level of plasma sugar continued. It has since been possible to make a further increase to 55 gm. protein, 10 gm. carbohydrate and 1200 calories.

Discussion: The history suggests that the diabetes may have originated in an acute infection. The patient enjoyed the advantages of strict care under eminent medical supervision from the time of the first diagnosis, six weeks after the apparent onset of the disorder. The record for the first four and a half years is one of typical downward progress, first on liberal diets corresponding to the mild diabetes, later on increasingly severe restrictions proportioned to the increasing severity of the diabetes. Violations of diet were absent throughout. The steady decline of tolerance and increasing tendency to glycosuria must be explained by one of two causes; either a progressiveness of the underlying diabetic process, or a slight prolonged overstrain of the weakened function indicated by the fact that the blood sugar was not kept normal, and the diet was forced to the point of occasional slight returns of glycosuria. On this program the patient had been brought to a point where

he faced an apparent dilemma of death from diabetes, or death from starvation. His diet of 50 gm. protein, 5 gm. carbohydrate, and 600 calories, with interspersed days of partial fasting, was too low to sustain life. So far from being able to increase the diet, he was unable to remain continuously free from glycosuria even on this starvation basis. He came to the Institute on account of this dilemma.

The treatment in the Institute was begun with more rigid under-nutrition. The emaciated patient was further reduced in weight by about 11 pounds. As previously stated¹, such a reduction of weight accomplishes three results: first, it abolishes glycosuria and hyperglycemia; second, it reduces the food requirement so that the same absolute ration is made relatively more adequate; third, it raises the food tolerance so that a higher absolute ration can be assimilated. In this way, this patient's tolerance was raised to a level (namely, 50 to 55 gm. protein, 5 to 10 gm. carbohydrate, and 1100 to 1200 calories) on which life could readily be supported. For two and a half years he has thus been kept free from hyperglycemia and glycosuria without further loss of either tolerance or weight. It will be noted that the tendency to hyperglycemia is distinctly less than at the beginning of treatment. The time elapsed is adequate for judgment, because there was no single year in the patient's previous record in which he had not suffered a definite decline of tolerance. Furthermore, this period of treatment was undertaken in the later stage of his progress, when the difficulties of control are known to be greater. The patient is weak and emaciated, but otherwise comfortable. He is up and walking about the greater part of every day, but is incapable of any useful work. Even with his medical training and strict fidelity, he probably could not conduct his treatment successfully at home, and for safety must live constantly in an institution. The conclusion is warranted that this case of diabetes was typically progressive under treatment which slightly overtaxed the assimilation, and thus far appears to be non-progressive under treatment which guards against any detectable functional overstrain.

Case No. 24.—Male; American; age 27; married; salesman.

Family history: There has been no known diabetes or obesity in the family. The patient's father died of pneumonia at 43. His mother is well except for a mild nephritis at 52. One brother, aged 32, is well. The patient has been married ten years. His wife and one son are healthy.

Past history: The patient had chicken-pox, measles, mumps, and whooping cough in early childhood, otitis media without complications at 8 years, and tonsillectomy at 15 years. He was found normal in a life insurance examination in 1912. His habits have been regular and healthful, without alcoholic indulgence or excesses in food. His height is 5 feet 6½ inches, and his maximum weight was 142 pounds at the age of 20.

Present illness: The first symptoms were polyphagia, polydipsia, polyuria, and weakness, which appeared acutely August 20, 1913. Dur-

ing the following three weeks, the weight fell from 138 to 130 pounds. A physician, who was then consulted, found glycosuria of 7 per cent., and immediately prescribed an old-fashioned abundant protein-fat diet, with buttermilk and gluten bread. Glycosuria and other symptoms gradually diminished during a month of this diet, and he then was free from glycosuria for the following three months, while his weight fell to 120 pounds. This same plan of diet was followed throughout 1914, 1915 and 1916. Glycosuria sometimes returned spontaneously, and at other times the patient broke diet, but always cleared up his sugar promptly by fasting for a day or two on black coffee and two or three ounces of whiskey. The tendency to glycosuria gradually increased, and the control became more difficult. The weight likewise slowly fell to 115 pounds. In April, 1917, glycosuria ceased to be controllable and was continuous for the following year. Occasional fast days with whiskey and black coffee were still taken in order to reduce it. At other times, large quantities of carbohydrate were eaten in the form of oatmeal, bread, pie, and even sugar. The glycosuria was commonly 6 to 8 per cent., and the weight fluctuated between 110 and 105 pounds. The typical symptoms were distressing during this year, and weakness gradually increased. From January to April, 1918, he attempted to increase his weight and strength by giving up work and eating as much food as possible. Besides protein and carbohydrate, he consumed enormous quantities of fat, and on April 1 became acutely ill with nausea and drowsiness. He was admitted to a hospital in San Francisco, and put to bed on a low diet of protein and carbohydrate. The acidosis symptoms subsided, and within a month the diet was increased to 60 gm. protein, 80 gm. carbohydrate and 1400 calories. Glycosuria was absent, but blood sugar analyses were not performed.

In July, 1918, glycosuria returned on account of laxity in diet, and continued until September even though the diet of 1400 calories was observed. In September, he entered a hospital in Salt Lake City, where two days of fasting were required to stop glycosuria. Within a month the diet was gradually increased to 55 gm. protein, 20 gm. carbohydrate and 1100 calories. Glycosuria remained absent for a month at home, but reappeared November 1, and remained constant until December 17 without violation of diet. At that time the patient came East for consultation regarding his serious condition. By a month of very low diet, interspersed with fast days, his plasma sugar was reduced to 0.150 per cent. with glycosuria constantly absent, but the tolerance appeared to be only 40 gm. protein and 500 calories. Living at the home of a relative in New Jersey from February to August, 1919, his diet averaged 500 to 600 calories daily, with absence of glycosuria except for two brief violations of diet. On July 28 he deliberately ate unlimited quantities of a mixed diet, with the result that heavy glycosuria was present at his admission to the Institute on August 4.

Physical examination: The physical examination was negative except for emaciation and anemia. The blood pressure was 116/78. His record in the Institute is shown in table II.

The glycosuria was cleared up by diets of less than 500 calories, interspersed with fast days, and by August 25 the plasma sugar had become normal. In September, hyperglycemia resulted from attempts to raise the diet to 60 gm. protein and 1000 calories. October 13 the patient was seriously weak, with plasma sugar at the dangerously low level of 0.04 per cent. The diet was immediately raised to 60 gm. protein, 5 gm. carbohydrate and 1000 calories on October 14, and to 60 gm. protein, 20 gm. carbohydrate and 1200 calories on October 16, with resulting hyperglycemia of 0.211 per cent. A fast day on October 19 reduced this to the dangerously low level of 0.05 per cent. During this time the patient complained of pains, apparently of ureteral origin. Several small calculi were passed, the urine became scanty and contained much pus and blood, and the blood urea rose to a maximum of 242 mg. per 100 cc. on November 17. The body weight, which on October 17 had reached a minimum of 73 pounds due to undernutrition, rose by edema to 90 pounds on November 30. The existing anemia was intensified so that the red cell count fell to 1,400,000 on November 18. Slight febrile reactions were present, but the temperature never went above 100.6° owing to the state of weakness. The patient was bed-fast in such a state of extreme prostration and intoxication that he was unable to lift his head from the pillow. The question was debated whether to ignore the diabetes and feed for the sake of strength. Inasmuch, however, as feeding a severely diabetic patient does not confer any real or lasting strength, a strict dietary regime was continued. The protein allowance was reduced to conform to the nitrogen retention, no more than 40 gm. per day being allowed. Carbohydrate was likewise restricted to 5 or 3 gm. because of the tendency to hyperglycemia. The calories were made up with fat, generally to a total of 1000 daily. Radiograms revealed one small shadow located in the left ureter near the bladder. This shadow disappeared when the patient passed a calculus of the approximate size and shape of a small orange seed. All the symptoms then gradually improved, though the urine still contained much albumin and pus. It was possible to keep the blood sugar regularly normal, though the blood urea continued above normal. As the patient craved protein, this was increased to 50 gm. and occasionally 60 gm. daily. As the tolerance improved, the carbohydrate was increased sometimes as high as 25 to 35 grams. Increase of calories as high as 1200 or 1300 was sometimes attempted, but hyperglycemia resulted, and the patient was never able to tolerate more than 1000 or 1100 calories. From October 3 to December 31, 1921, the patient was used for experiments, first with fat and then with alcohol, as described by Leclercq³. Hyperglycemia and traces of glycosuria resulted in the following months, and prolonged reduction of diet was necessary to atone for the injury thus caused. The patient has now become able to tolerate a diet of 45 gm. protein, 10 gm. carbohydrate and 900 calories, but the tolerance for 1000 or 1100 calories, which existed before the over-nutrition experiment, has not been regained, and it is not certain whether the injury may be permanent. The urine now contains only traces of albumin, but the blood urea re-

mains elevated, generally between 60 and 80 mg. per 100 cc. The patient is particularly energetic by nature and manages to carry on very light duties during the greater part of every day.

Discussion: This case represents downward progress under the old-fashioned plan of diet for three years. This was not checked by the short subsequent periods of partially efficient control, especially as these were interrupted by violations of diet. The patient was received when emaciated to 93 pounds and apparently unable to maintain normal blood sugar on a diet of 40 gm. protein and 500 calories, which was insufficient to support life. Fasting and undernutrition were applied so as to reduce the weight by perhaps 15 or 20 pounds, the uncertainty being due to irregularities in water retention. The control of the diabetes was continued as strictly as possible through a period of extreme weakness and intoxication due to pyelonephritis. A tolerance was gradually built up for a living diet of 1000 or 1100 calories. This tolerance was perceptibly damaged by a short period of attempted overnutrition. There has been no perceptible downward progress from any other cause. The tolerance is still definitely higher than at admission, and the diet suffices to maintain weight and nitrogen equilibrium. The case is so severe that the margin of safety is very narrow. No further attempt at over-feeding with fat or alcohol can be risked, and any slight injury, such as a minor infection, might reduce the tolerance so low that life could not be maintained. This patient also cannot live except under institutional conditions, as slight errors in diet at home would make downward progress certain. No element of inherent progressiveness has been apparent in more than two and a half years of observation in this Institute. The diabetes also creates no difficulty in carrying out a low protein, low salt diet for the nephritis.

Case No. 41.—Male; Irish-American; age 33; single; millinery salesman.

Family history: The family are ignorant, but are not aware of any diabetes, obesity or nephritis among their relatives. The father is well at 72. The mother died at 36 of heart disease. One brother, aged 33, and one sister, aged 28, are well.

Past history: The patient has always been small, frail and thin. He had measles, diphtheria, chicken-pox and whooping cough before the age of 10. At 7 years he had a severe lobar pneumonia with protracted convalescence. At 18 years he suffered from dyspnea, precordial pain and palpitation, and a physician diagnosed endocarditis. These symptoms were distressing for one year, but after that he performed light work and enjoyed fairly good health until the age of 25. He then had acute gangrenous appendicitis with operation and drainage for three weeks. He had gonorrhea in 1913, but denies syphilis by name and symptoms. For the past four years he has suffered from what he calls hay fever. His appetite has always been good, and he has used small quantities of beer and whiskey, but there have been no excesses in either food or drink. He is of nervous disposition, concentrates his

effort and worry upon his work, but sleeps well. With a height of 5 feet 8 inches, he has weighed about 120 pounds, never over 125.

Present illness: During May, 1918 he noticed fatigue and irritability, and the loss of 2 or 3 pounds of weight. From June 10 to August 10 he took his summer vacation, but failed to regain strength as anticipated. He continued work with difficulty until the marked onset of polyphagia, polydipsia and polyuria in September, when his weight had fallen to 112 pounds, and his family physician diagnosed diabetes. Glycosuria ceased after a complete fast of thirty-six hours. It remained absent during the following four months on an unweighed diet of proteins, fats, and low-carbohydrate vegetables and fruits. The body weight meantime diminished to 108 pounds. In September, 1918 his blood pressure was found to be 218 systolic, 136 diastolic. There was albuminuria of one and a half to three grams per liter, with numerous hyalin and granular casts. He had frequent dyspnea and palpitation on exertion but no edema. In April, 1919 he had a slight apoplectic stroke involving the entire left side, but he recovered complete function after eleven weeks in bed. The blood pressure during this period of strict bed rest ranged from 185 to 220 systolic and 110 to 130 diastolic. A low protein diet, with abundant fat and moderate carbohydrate, was prescribed during this period. Glycosuria was constant during April, May, and June, 1919, and hunger, thirst, and weakness were distressing. By June 20 his weight had fallen to 93 pounds. In July, 1919 an accurately weighed diet was undertaken, of 60 gm. protein, 40 gm. carbohydrate and 1000 calories, but glycosuria was continuous, and the weight by August 17 had fallen further to 87 pounds.

Physical examination: The patient was poorly nourished and emaciated, and with a height of 5 feet 8 inches weighed 87 pounds. His eyes reacted normally. On examination of the eyegrounds, the arteries were found to be small and tortuous, but no hemorrhages could be seen. The disc outlines were blurred and indistinct. Nose, ears, throat and tonsils were normal. The thorax was long and narrow, of typical pigeon breast type. The heart was enlarged to the left, the apex beat 3 cm. outside of MC line. There was a marked diffuse precordial bulge. The heart action was regular. There was a marked systolic murmur at the apex, transmitted to the axilla and over the whole precordia. The aortic second sound was increased, the heart rate 96 per minute, the blood pressure 206/160. The liver and spleen were not palpable. Reflexes were present and equal. The blood urea was 134 mg. per 100 cc., plasma chloride 576 mg. per 100 cc., and carbon dioxide combining power of plasma 61.5 vol. per cent. The Wassermann test was negative. The urine contained 2 gm. albumin per liter, with numerous hyalin and granular casts.

The patient's record in the Institute is shown in table III.

The diet at first was directed chiefly to the nephritis, and was a ration of 30 gm. protein, 30 gm. carbohydrate and 1200 calories a ration of 30 gm. protein, 30 0gm. carbohydrate and 1200 calories was instituted. The low protein was necessary on account of the nitrogen retention. The 1200 calories, composed chiefly of fat, main-

tained weight and strength and prevented loss of body protein. The 30 gm. of carbohydrate sufficed to prevent acidosis. The blood pressure was reduced by the salt-free diet, but not to normal. Symptoms were relieved to such an extent that after discharge on November 24 the patient resumed his ordinary light work, first for half time daily, and later for full time. He was re-admitted to the Institute, July 25 to September 14, 1920 for observation, and resumed work after discharge. On December 20 he was again admitted on account of an infected wound. As the plasma sugar was 0.231 per cent., stringent undernutrition was used to reduce it in order to favor healing. The patient again resumed work after his discharge on January 4, 1921, and continued up to his readmission on June 19. Evident symptoms of uremia were then present. He could eat little at this time; treatment was unavailing; weakness and intoxication rapidly progressed, and death occurred in coma without convulsions on June 27.

Discussion: Though this patient was young, the diabetes was not of the highly progressive type. As it was evident from the outset that the cardiorenal disease was the most threatening condition, no attempt was made to maintain constantly normal blood sugar, but the patient was merely kept continuously free from glycosuria with moderate limitation of the blood sugar, on a diet planned chiefly to guard his nephritis and to maintain strength and nutrition. The body weight was thus kept approximately even during the greater part of two years. The food tolerance apparently fell slightly, as judged by the fact that the blood sugar was distinctly lower on a diet of 30 gm. protein, 30 gm. carbohydrate and 1200 calories from September to November, 1919 than on lower diets from January to June, 1921. This slight fall of tolerance is sufficiently explained by the slight overload of the assimilation, and no inherently progressive element need be assumed. As anticipated, death occurred from nephritis before the downward tendency in the diabetes had become serious. Under the circumstances the slight overload of the assimilation for the sake of greater temporary comfort and strength is considered justified.

Case No. 54. — Female; American; age 39; single; school teacher.

Family history: No cases of diabetes, obesity or nephritis have been known in the family. The father was drowned when healthy at the age of 61. The mother is living at 70 years, but has been an invalid with severe arthritis deforms for the past ten years. Two brother died in infancy. One sister died at 31 of exophthalmic goitre, and another at 42 of brain tumor. One sister is living and well; another living but sickly, with suspicion of tuberculosis.

Past history: The patient had measles, mumps, whooping cough and chicken-pox in childhood. Between the ages of 16 and 20 she suffered from asthma. During this time she also had attacks of severe pain in the lower abdomen, accompanied by fever. At the age of 20 she underwent appendectomy, bilateral oöphorectomy, and suspension. At the age of 38 she had pleurisy for two weeks, but has never been subject to coughs or colds. The habits have been regular and normal

without excesses of any kind. Her work as a teacher has involved some nervous strain. With a height of 5 feet 8 inches she has had an average weight of 130 pounds, and a maximum of 135 pounds at the age of 38. Constipation has been habitual.

Present illness: During the six months preceding October, 1918, the patient lost 10 pounds without noticing that anything was wrong. The first symptom noticed was acute thirst and polyuria on October 3, followed by partial blindness the next day. A physician then called found 5 per cent. glycosuria. He immediately prescribed a diet of lean meats and green vegetables, on which glycosuria, polyuria and visual disturbance cleared up in three days. From this time until March, 1919 she remained on an unweighed diet of meat, fish, eggs, 5 per cent. vegetables and fruits, with large amounts of butter and cream, without fast days. The weight slowly fell to 110 pounds. Occasional traces of glycosuria were checked by partial fast days. After March the carbohydrate had to be restricted more closely in order to check the increasing tendency to glycosuria. Sugar was never allowed to be present in more than traces or for a longer time than one day. An increasing number of fast days became necessary for this purpose, and by July the weight had fallen to 103 pounds. She also became seriously weakened, but managed to complete her term of school.

In August, 1919 she changed to another physician, who prescribed a high caloric diet, with abundance of both carbohydrate and fat, for the purpose of increasing her weight. Heavy glycosuria resulted, the weight fell to 97 pounds, and on September 1 she became acutely ill with nausea, weakness, drowsiness and epigastric pain. Another physician reduced the diet, but could not bring the symptoms under control, and the patient accordingly was admitted to the Institute on September 28, 1919.

Physical examination: The physical examination was negative, except for emaciation and signs of acidosis. The blood pressure was 122/79. The further report is contained in table IV.

Treatment was begun with two days of fasting, followed by low calory diets consisting chiefly of protein and carbohydrate. The diet was gradually built up so that on December 23 the patient was discharged on 40 gm. protein, 5 gm. carbohydrate and 1000 calories, with one day of complete fasting each week. She remained at her home in the country without blood analyses until April 28, and returned in good condition. June 28 she was discharged on 50 gm. protein, 5 gm. carbohydrate and 1050 calories, with normal plasma sugar of 0.118 per cent. She again remained faithful to diet at her home in the country, but from September to November had occasional returns of glycosuria. These were more and more difficult to control, until on November 29 she returned to the Institute with heavy glycosuria. With a diet of only 10 gm. protein daily, broken by two fast days, glycosuria quickly ceased, but hyperglycemia was still present on December 18. With very slight increase of diet to 40 gm. protein and 400 calories, a normal level of plasma sugar was regained on January 4, 1921. The diet for the ensuing months remained extremely low. By the close of

April, the former level of 1050 calories was regained, but the weight was then 66 to 70 pounds, as against 82 to 84 pounds when the patient had tolerated this same diet a year previously. The attempt to raise the diet to 1100 calories in May proved unsuccessful. Owing to the progressive character of the case, much lower diets of 600 to 900 calories were resumed in June and July. In August, the attempt to raise the ration to 1100 calories again resulted in hyperglycemia, requiring a further undernutrition period in September and October. The difficulty in this instance was not due so much to the fact that the patient was at home from August 12 to September 9, as to the excessive caloric allowance. The patient has since remained continuously in the Institute. Her weight is only 62 pounds. She can assimilate no higher diet than 45 gm. protein, 3 gm. carbohydrate and 800 calories, and on this there is still a tendency to hyperglycemia. She is a complete invalid, spending most of her time in bed and the remainder in a wheel chair, and scarcely able to walk or stand. Her hunger is satisfied by the use of the usual bulky foods, so that she remains cheeful, with no complaint except weakness.

Discussion: This case illustrates the late, extremely severe stage of a case of markedly progressive diabetes. It proved possible to build up the tolerance to 1000 or 1050 calories with normal blood sugar. A tolerable state of invalidism might have been supported on this diet. Trouble resulted from attempts to give slightly excessive diets, and especially from the continuance of such diets for considerable periods at home where blood tests were not performed. The period of three months, September to November, 1920, characterized by repeated returns of glycosuria, was particularly disastrous in this respect, and thereafter the former tolerance was never regained. A period of such injury is extremely serious for a patient whose assimilation barely suffices to maintain life. It is possible that the tolerance has thus been reduced slightly below a living ration, and that indefinite maintenance of life has therefore become impossible. No decline of assimilation, except that resulting from the dietary overstrain, has been perceptible in this case.

Case No. 23. — Male; American; age 15; single; schoolboy.

Family history: The mother, father and one sister are living and well. No cases of diabetes, obesity or metabolic disorders have been known in the family.

Past history: The patient had measles and mumps before the age of 9. Otherwise, he has been a very strong, healthy boy, completely free from infections or other ailments, with a normally large appetite for sweets and starches. With a height of 5 feet 6 inches, his highest weight was 96 pounds without clothes.

Present illness: About January, 1918, the parents became aware that the boy had been showing thirst and polyuria, and losing slightly in weight for a month or two. On advice of the family physician, he was taken from school and given milk and the richest possible diet for the purpose of building up his weight. Polydipsia, polyuria and

loss of weight increased. A curious features is that seven urinalyses by two or three different physicians or laboratories between May, 1918 and May, 1919, were all reported negative, though the symptoms leave little doubt of the existence of typical diabetes. On account of failing vision, he consulted an oculist in May, 1919, who diagnosed double diabetic cataract and referred him to a consultant, who found heavy glycosuria and acetonuria, and gave a prognosis of early death. The weight had fallen to 75 pounds. Treatment failed to control symptoms until in July, 1919, the patient was taken to a hospital and made free from glycosuria by six days of continuous fasting. The sugar returned with every attempt to give any diet. When the patient was seen in consultation July 31, 1919, heavy sugar, nitroprusside and ferric chloride reactions were found in the urine, the lipemic plasma resembled cream, the plasma sugar was 0.441 per cent., and the CO_2 capacity 68 vol. per cent. The last figure was explained by the use of alkali; the plasma gave a heavy nitroprusside reaction. Alternation of fasting and a very low protein diet was advised, and the patient was admitted to the Institute on August 5. He then weighed 66 pounds and was markedly drowsy. The cataracts caused almost complete blindness.

Physical examination: The physical examination was negative except for cataracts, emaciation, and absence of knee reflexes.

The further record is shown in table V.

Notwithstanding the extreme weakness and emaciation, fasting and low diets were imposed as usual, until a normal level of plasma sugar was attained on September 15. Attempts to increase the diet brought returns of hyperglycemia, but the weakness appeared so threatening that moderate degrees of hyperglycemia were permitted in order to maintain as liberal a diet as possible. The patient was kept continuously in the Institute until April 3, 1920, when he was sent home on a carbohydrate-free diet of 40 gm. protein and 500 calories, with normal blood sugar. At home he was strictly faithful and kept continuously normal blood concentrations until July, while the diet was increased to 50 gm. protein, 3 gm. carbohydrate and 700 calories. Then, apparently on account of a cold, faint glycosuria appeared, and he was immediately readmitted to the Institute. The ease with which the blood sugar was brought to normal at this time contrasts with the first admission, and the patient was discharged August 5 on a diet of 50 gm. protein, 1 gm. carbohydrate and 600 calories. The difficulties at home were greater than before, and he re-entered the Institute on September 22 because of a return of hyperglycemia and glycosuria. He was again discharged October 3, and readmitted November 1. Other discharges and readmissions are shown in the chart. In each instance, the trouble resulted not from an error or violation of diet, but from slight infections (cold in two instances, and a diarrheal attack on another occasion). The latter attacks occurred while the patient was directly under observation in the Institute in the first half of June, 1921. Faint to heavy glycosuria is shown in the chart for that period, and thereafter the tolerance was never above 35 gm. protein, 5 gm. carbo-

hydrate and 500 calories. Death occurred from inanition on August 13, 1921.

The case represented the most extreme, hopeless type of juvenile diabetes. The boy had continued to lose weight and strength, both on high feeding, and on carefully restricted diets which allowed glycosuria to persist. When first seen, his possible duration of life was estimated by the physician in charge at about two weeks. The following benefits were accomplished by a rigorous undernutrition treatment: first, the patient actually lived two years; second, he was enabled to undergo successful operations for his cataracts, so that fully satisfactory vision was restored in both eyes; third, instead of being confined to bed as formerly, he gained sufficient strength to be up most or all of every day until April, 1921, and to go on automobile rides and enjoy other pleasures. On the other hand, he never attained anything more than a state of invalidism, and the attempt to maintain his life failed after two years of intense effort on the part of himself and his family. The progress was of two kinds: first, the usual rise of assimilation with the initial undernutrition; the body weight remained practically unchanged up to April, 1920, but the loss of tissue was masked by water retention; a normal level of blood sugar was thus obtained; second, downward progress was observed in connection with at least three minor infections, of which the most serious one was intestinal. The change in the tolerance was actually slight, and the fatal outcome was explainable not by progressiveness of the diabetes, but by the degree of severity already present when the patient was first seen, which precluded the assimilation of any diet which would permanently support life. Such severity may make a fatal outcome inevitable, even though any further aggravation of the diabetes be prevented. The case fails to show any inherent progressiveness, even in the most severe form of juvenile diabetes.

CONCLUDING REMARKS.

Evidence has previously been presented in favor of the view that diabetes represents the weakened function of a damaged organ, that the aim of treatment is to spare this weakened function so as to prevent its further impairment by overstrain, and that the blood sugar affords a more delicate index of functional overload than urine tests. The strictest control, to the point of continuously normal blood sugar concentration, is most important in the cases which are inherently most progressive. This result may require continuous institutional care in unusually extreme cases. The errors and irregularities of home conditions generally deprive observations on ambulant patients of scientific conclusiveness.

The records of these five patients with the youthful severe

type of diabetes are presented, partly because obtained so largely under conditions of strict institutional supervision. They appear to be in no way exceptional, but on the contrary to correspond fully with the conditions in several hundred other patients observed during the same period, in so far as it has been possible to keep these others under exact dietetic control. These observations are opposed to the belief in a mysterious, spontaneous progressiveness of typical diabetic cases. They support the view that functional deterioration in diabetes can be traced to definite causes, particularly infections and dietary excesses, that downward progress clinically depends upon the different susceptibilities of different patients to these injurious influences, and that by the strict avoidance of such influences downward progress can be largely or wholly prevented.

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TABLE I.
Case No. 85.

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
1919								
November								
5	fast	day	—	0	0	272	111	Admitted
6 & 7	50	—	—	0	0	—	—	
8	30	—	127	0	0	150	109	
9 to 11	30	—	—	0	0	—	—	
12	30	—	200	0	0	101	107	
13 to 15	40	—	500	0	0	107	—	
15 to 20	50	—	800	0	0	102	103	
20	50	—	800	0	0	101	101	
21 to 26	50	5	900	0	0	—	98	
26 to 30	50	10	900	0	0	101	96	
December								
1	60	10	1000	0	0	87	98	
2 to 5	60	10	1000	0	0	—	97	
6	60	10	1000	0	0	92	—	
6 to 11	60	15	1400	0	0	—	—	Weekly fast days 10P, 5CH.
12	60	15	1400	0	0	118	101	Weekly fast days 10P, 5CH.
13 to 18	60	15	1400	0	0	—	99	Weekly fast days 10P, 5CH.
19	60	15	1400	0	0	220	99	Weekly fast days 10P, 5Ch.
20 to 29	60	5	1200	0	0	—	100	Weekly fast days 10P, 5Ch.
30	60	5	1000	0	0	197	100	Weekly fast days 10P, 5CH.
31	60	5	1200	0	0	—	—	
1920								
January								
1 to 4	60	5	1200	0	0	—	100	
5	60	5	1200	0	0	184	102	
6 to 8	55	5	1200	0	0	—	101	
8	50	3	972	0	0	—	101	
9	50	3	972	0	0	—	101	
10	35	2	850	mod.	faint	429	102	
11	fast	day	—	0	0	159	101	
12	fast	day	—	0	0	140	101	
13	36	5	557	0	0	90	101	
14	33	5	449	0	0	142	101	
15	35	5	648	0	0	131	—	
16 to 17	33	5	600	0	0	—	102	
18	12	—	—	0	0	—	—	
19	43	5	850	0	0	91	101	
20 to 23	45	5	800	0	0	—	102	
24	50	5	1000	0	0	—	102	
25	20	—	—	0	0	—	—	Fast day.
26	50	5	1000	0	0	—	—	
27	50	5	1000	0	0	142	104	
28	do	—	—	0	0	—	105	
29	50	5	1000	0	0	—	107	
30	do	—	—	0	0	250	108	
31	do	—	—	0	0	—	110	

TABLE I. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
February								
1	10	—	—	0	0	—	112	Fast day.
2 to 8	50	5	1000	0	0	—	112	
8	20	—	—	0	0	—	—	Fast day.
9	50	5	1000	0	0	156	109	
10	50	5	1000	0	0	—	108	
11	do	—	—	mod.	0	—	—	
12	20	—	—	faint	0	—	—	Fast day.
13	fast	day	—	0	0	117	102	
14	20	—	—	0	0	—	—	Fast day.
15	50	5	900	0	0	—	103	
16 & 17	50	5	800	0	0	—	103	
18	do	—	—	0	0	250	103	
19	do	—	—	0	0	—	—	
20	do	—	—	faint	0	319	104	
21	15	—	—	faint	0	—	105	Fast day.
22	15	—	—	0	0	—	106	Fast day.
23	50	—	600	0	0	—	107	
24	50	—	596	0	0	214	—	
25 & 26	do	—	—	0	0	—	—	
27	do	—	—	0	0	225	108	
28	do	—	—	0	0	—	—	
29	20	—	150	0	0	—	107	Fast day.
March								
1	20	—	150	0	0	152	—	Fast day.
2	20	—	150	0	0	—	109	Fast day.
3	20	—	150	0	0	137	—	Fast day.
4	20	—	150	0	0	—	—	Fast day.
5	20	—	150	0	0	112	111	Fast day.
6 & 7	40	3	500	0	0	—	112	
8	40	3	600	0	0	—	—	
9	40	3	500	0	0	147	107	
10 & 11	40	3	550	0	0	—	107	
12	40	3	550	0	0	75	—	
13	40	3	700	0	0	—	105	
14	20	—	—	0	0	—	—	Fast day.
15	do	3	800	0	0	—	104	
16	50	—	—	0	0	84	—	
24 & 25	50	3	1000	0	0	—	108	
26	do	—	—	0	0	132	110	
28 to 31	do	—	—	0	0	—	112	
April	50	3	1100	0	0	94-131	110	Weekly fast day of 20 Protein.
May								
1 to 13	60	3	1200	0	0	62-123	112	Weekly fast day of 20 Protein.
14	do	—	—	0	0	198	115	
15 to 17	60	3	1200	0	0	—	112	
18	do	—	—	0	0	91	—	
19	do	—	—	0	0	—	—	
20	do	—	—	faint	—	—	—	
21	do	—	—	faint	—	207	—	
22 to 31	50	3	800	0	0	88-142	114	Weekly fast day of 20 protein.
June								
1 to 12	50	3	800	0	0	82-140	115	Weekly fast day of 20 protein.
12 to 23	50	3	1000	0	0	81	118	Weekly fast day of 20 protein.
24	50	3	1200	0	0	—	116	

TABLE I. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
June-Con.								
25	do	—	—	0	0	161	116	
26	do	—	—	0	0	201	—	
27	do	—	—	faint	faint	273	—	
28	do	—	—	faint	faint	315	—	
29	do	—	—	mod.	slight	322	115	
30	do	—	—	mod.	faint	371	117	
July								
1	30	1	700	faint	0	337	118	
2	20	—	—	0	0	193	119	
3	20	—	188	0	0	154	120	
4	20	—	188	0	0	135	120	
5	50	3	800	0	0	180	—	
6	do	—	—	0	0	—	—	
7	24	—	411	0	0	147	—	
8	do	—	—	0	0	—	120	
9	50	3	800	0	0	138	—	
10	do	—	—	0	0	—	—	
11	20	—	—	0	0	—	—	
12	50	3	800	0	0	—	—	
13	50	—	—	0	0	157	120	
14	50	—	—	0	0	—	—	
15	50	—	—	0	0	100	—	
16	50	—	—	0	0	—	—	
17 to 20	50	3	900	0	0	—	120	
July								
18	20	—	—	0	0	—	120	Fast day.
19 & 20	50	3	900	0	0	—	119	
21	do	—	—	0	0	114	118	
22 to 24	do	—	—	0	0	—	117	
25	20	—	—	0	0	—	115	
26	50	3	900	0	0	82	114	
27 & 28	50	3	900	0	0	—	112	
29 to 31	50	3	1000	0	0	—	—	
August								
1	20	—	—	0	0	—	113	
2	50	3	1000	0	0	—	—	
3	50	3	1000	0	0	122	113	
4 & 5	do	—	—	0	0	—	—	
6	do	—	—	0	0	111	110	
7 to 12	do	—	—	0	0	—	—	
13	do	—	—	0	0	179	112	
14 to 19	do	—	—	0	0	—	—	One fast day of 20 protein.
20	20	—	—	0	0	166	111	Fast day.
21	do	—	—	0	0	—	—	Fast day.
22	do	—	—	0	0	—	110	Fast day.
23 to 26	50	3	900	0	0	—	110	
27	30	1	—	mod.	0	362	—	Fast day.
28 & 29	20	—	—	0	0	—	107	Fast days.
30	20	—	—	0	0	170	—	Fast day.
31	20	—	—	0	0	111	109	Fast day.
September								
1 & 2	50	2	700	0	0	—	109	
3	30	2	550	0	0	204	—	
4	20	—	—	0	0	—	110	Fast day.
5	20	—	—	0	0	161	—	
6	20	—	—	0	0	—	110	
7	50	2	700	0	0	98	—	
8 & 9	do	—	—	0	0	—	110	

TABLE I. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight, Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Sept.-Con.								
10	do	—	—	0	0	174	—	
11 & 12	20	—	—	0	0	—	110	
13	50	—	700	0	0	90	—	
14 to 17	50	—	700	0	0	—	110	
17	do	—	—	0	0	179	—	
18 & 19	40	—	—	—	—	—	110	
20	40	—	268	0	0	181	110	
21	40	—	250	0	0	168	—	
22	40	—	259	0	0	—	110	
22 & 23	40	—	259	0	0	—	—	
24	40	—	295	0	0	120	—	
25	40	—	223	0	0	—	107	
26	40	—	900	0	0	99	—	
27	40	—	900	0	0	—	106	
28	40	—	900	0	0	145	—	
29	40	—	900	0	0	—	104	
30	30	—	900	0	0	219	103	
October								
1 & 2	30	—	200	0	0	—	—	
3	30	—	200	0	0	139	101	
4 to 6	40	2	400	0	0	—	—	
7	45	2	500	0	0	115	101	
8 & 9	45	2	900	0	0	—	—	
10	do	—	—	0	0	102	102	
11	do	—	—	0	0	—	103	
12	do	—	—	0	0	159	—	
13	do	—	—	0	0	176	104	
14	30	2	400	0	0	—	—	
15	do	—	—	0	0	113	104	
16	40	2	500	0	0	—	—	
17 & 18	do	—	—	0	0	—	103	
19	do	—	—	0	0	106	—	
20 & 21	40	2	600	0	0	—	103	
22	50	3	700	0	0	86	—	
23	do	—	—	0	0	—	103	
24	30	—	—	0	0	—	—	Fast day.
25	50	3	700	0	0	—	102	
26	50	3	800	0	0	82	—	
27 & 28	50	3	800	0	0	—	101	
29	50	3	900	0	0	93	—	
30	do	—	—	0	0	—	101	
31	30	—	—	—	—	—	100	Fast day.
November								
1	50	3	900	0	0	—	—	
2	do	—	—	0	0	109	—	
3	50	5	900	0	0	—	98	
4	do	—	—	0	0	135	—	
5 & 6	do	—	—	0	0	—	100	
7	30	—	—	—	—	—	—	Fast day.
8	50	5	900	0	0	—	100	
9	do	—	—	0	0	170	—	
10	40	5	400	0	0	—	102	
11	40	2	500	0	0	101	—	
12	50	2	600	0	0	85	102	
13 to 15	do	—	—	0	0	—	—	
16	50	2	700	0	0	104	105	
17 & 18	do	—	—	0	0	—	—	
19	do	—	—	0	0	185	106	

TABLE I. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Qualitative Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Nov.-Con.								
20	do	—	—	0	0	—	—	
21	30	—	—	0	0	95	106	Fast day.
22 to 25	50	2	700	0	0	—	—	
26	50	2	700	0	0	188	108	
27	50	2	700	0	0	—	110	
28	30	—	—	0	0	—	—	Fast day.
29	50	2	700	0	0	101	110	
30	do	—	—	0	0	101	110	
December								
1 & 2	50	2	800	0	0	—	108	
3	do	—	—	0	0	103	107	
4	do	—	—	0	0	—	106	
5	30	—	—	0	0	—	—	Fast day.
6	50	2	800	0	0	—	105	
7	do	—	—	0	0	146	—	
8	30	—	—	0	0	—	106	Fast day.
9	50	3	700	0	0	89	—	
10 & 11	50	3	800	0	0	—	105	
12	30	—	—	0	0	—	—	Fast day.
14 to 20	50	3	700	0	0	—	106	
21	do	—	—	0	0	187	—	
22	30	1	—	0	0	—	106	Fast days.
23	30	1	—	0	0	—	—	Fast days.
24	50	3	600	0	0	—	105	
25	do	—	—	0	0	103	—	
26	do	—	—	0	0	—	105	
27	do	—	—	0	0	—	—	
28 to 30	do	—	—	0	0	—	106	
31	do	—	—	0	0	110	—	
							107	
1921								
January								
1	50	3	700	0	0	—	107	
2 to 4	50	3	700	0	0	—	—	
5	do	—	—	0	0	147	106	
6	30	—	—	0	0	—	—	Fast day.
7	50	3	600	0	0	—	—	
8 & 9	do	—	—	0	0	—	107	
10	do	—	—	0	0	116	—	
11 to 13	50	3	850	0	0	—	—	
14	do	—	—	0	0	113	106	
15	30	5	—	0	0	—	—	Fast day.
16 to 20	50	3	850	0	0	—	—	
21	30	5	—	0	0	—	—	Fast day.
22	50	3	900	0	0	—	106	
23	50	3	900	0	0	117	—	
24	do	—	—	0	0	105	—	
25 & 26	do	—	—	0	0	—	107	
27	25	5	—	0	0	—	—	
28	50	3	900	0	0	102	—	
29	50	3	1000	0	0	—	106	
30	do	—	—	0	0	—	—	
31	do	—	—	0	0	—	106	
February								
1 to 7	50	5	1000	0	0	—	108	
8	30	5	—	0	0	—	—	Fast day.
9 to 11	50	5	1000	0	0	—	109	
12	do	—	—	0	0	—	—	
13	do	—	—	0	0	133	109	

TABLE I. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Feb.-Con.								
14 to 16	do	—	—	0	0	—	—	
17	30	5	—	0	0	—	111	Fast day.
18	50	5	1000	0	0	—	—	
19	do	—	—	0	0	169	—	
20	45	5	900	0	0	—	111	
21	45	5	900	0	0	—	—	
22	45	5	900	0	0	134	109	
23	45	5	900	0	0	—	—	
24	45	5	900	0	0	187	—	
25	30	5	—	0	0	—	108	Fast day.
26	40	5	800	0	0	—	—	
27 & 28	do	—	—	0	0	—	108	
March								
1	45	5	800	0	0	—	107	
2	30	2	—	0	0	—	—	Fast day.
3	45	5	800	0	0	—	—	
4	do	—	—	0	0	116	108	
5 & 6	do	—	—	0	0	—	—	
7	do	—	—	0	0	133	—	
8	do	—	—	0	0	—	107	
9	30	3	—	0	0	—	—	Fast day.
10	45	5	800	0	0	—	—	
11 & 12	45	5	800	0	0	—	—	
12	do	—	—	0	0	98	108	
12	do	—	—	0	0	—	—	
13	45	5	900	0	0	—	—	
14	do	—	—	0	0	—	107	
15	30	1	—	0	0	—	—	Fast day.
16	45	5	900	0	0	100	107	
17 to 20	do	—	—	0	0	—	—	
21	do	—	—	0	0	—	—	
22	30	3	—	0	0	—	107	Fast day.
23 to 24	45	5	900	0	0	—	—	
25	do	—	—	0	0	118	108	
26 to 29	45	5	900	0	0	—	—	
30	30	1	—	0	0	—	109	Fast day.
April								
1	50	5	1000	0	0	104	109	
2	do	—	—	0	0	—	—	
3 to 5	do	—	—	0	0	—	—	
6	30	1	—	0	0	—	—	Fast day.
7	50	5	1000	0	0	—	—	
8	do	—	—	0	0	111	—	
9 & 10	do	—	—	0	0	—	—	
11	do	—	—	0	0	106	—	
12	55	5	1100	0	0	—	—	
13	30	1	—	0	0	—	—	Fast day.
14	55	5	1100	0	0	108	110	
15 to 18	do	—	—	0	0	—	—	
19	do	—	—	0	0	121	111	
20	30	1	—	0	0	—	—	Fast day.
21	55	5	1100	0	0	—	110	
22 & 23	do	—	—	0	0	—	—	
24	do	—	—	0	0	114	112	
25 & 26	do	—	—	0	0	—	—	
27	30	1	—	0	0	—	111	Fast day.
28	55	5	1100	0	0	—	—	
29	do	—	—	0	0	123	112	
30 & 31	do	—	—	0	0	—	112	

TABLE I. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
May								
1	30	1	—	0	0	112	112	Fast day.
2 to 5	60	8	1100	0	0	—	—	
6	do	—	—	0	0	133	—	
7	do	—	—	0	0	—	—	
8	30	1	286	0	0	—	—	Fast day.
9	60	8	1100	0	0	—	—	
10	60	8	1100	0	0	101	—	
11 to 13	60	8	1100	0	0	—	—	
13	do	—	—	0	0	108	—	
14	do	—	—	0	0	—	—	
15	30	1	322	0	0	—	—	Fast day.
16 to 20	60	10	1100	0	0	—	—	
20	do	—	—	0	0	214	—	
21	50	10	1000	0	0	—	—	
22	20	10	—	0	0	—	—	Fast day.
May								
1 to 6	60	8	1100	0	0	—	112	
6	do	—	—	0	0	—	—	
7	do	—	—	0	0	—	—	
8	30	1	286	0	0	—	112	Fast day.
9	60	8	1100	0	0	133	—	
10	do	—	—	0	0	101	—	
11 & 12	do	—	—	0	0	—	113	
13	do	—	—	0	0	108	—	
14	do	—	—	0	0	—	—	
15	30	1	322	0	0	—	112	Fast day.
16 to 20	60	10	1200	0	0	—	—	
20	do	—	—	0	0	214	—	
21	50	5	1000	0	0	—	—	
22	20	1	138	0	0	—	114	Fast day.
23	50	5	1000	0	0	—	—	
24 to 28	do	—	—	0	0	—	—	
28	do	—	—	0	0	101	115	
29	30	1	133	0	0	—	—	
30 & 31	50	5	1000	0	0	—	—	
June								
1 to 4	50	10	1000	0	0	—	—	
4	do	—	—	0	0	104	115	
5	30	1	314	0	0	—	—	Fast day.
6 & 7	55	10	1097	0	0	106	—	
8 to 11	55	10	1196	0	0	—	—	
11	do	—	—	0	0	114	114	
12	30	1	297	0	0	—	—	Fast day.
13 to 18	55	10	1200	0	0	—	117	
18	do	—	—	0	0	107	—	
19	30	1	275	0	0	—	118	Fast day.
20 to 25	55	10	1200	0	0	—	115	
25	do	—	—	0	0	119	115	
26	30	1	124	0	0	—	—	Fast day.
27 to 30	55	10	1200	0	0	—	115	
30	do	—	—	0	0	111	—	
July								
1 & 2	do	—	—	0	0	125	117	
3	30	1	126	0	0	—	—	Fast day.
4	55	10	1200	0	0	—	—	
5	do	—	—	0	0	127	120	
6	do	—	—	0	0	—	—	
7	45	10	1000	0	0	—	120	
8	45	10	1000	0	0	136	120	

TABLE I. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
July-Con.								
9	do	—	—	0	0	—	—	
10	30	1	139	0	0	—	—	Fast day.
11 & 12	45	10	1000	0	0	89	—	
13 & 14	50	10	1100	0	0	—	—	
15	do	—	—	0	0	83	—	
16	55	15	1300	0	0	—	—	
17	30	3	—	0	0	—	123	Fast day.
18	55	15	1300	0	0	—	—	
19	do	—	—	0	0	113	123	Faint lipemia.
20 to 23	do	—	—	0	0	—	—	
23	do	—	—	0	0	140	—	
24	30	10	—	0	0	—	—	Fast day.
25 to 30	50	10	1000	0	0	—	—	
30	do	—	—	0	0	106	112	
31	do	—	—	0	0	—	—	
August								
1 to 6	55	10	1100	0	0	—	113	
6	do	—	—	0	0	159	—	
7	13	10	—	0	0	—	—	Fast day.
8 to 13	45	10	900	0	0	—	—	
13	50	10	1100	0	0	117	—	
14	30	1	—	0	0	—	—	Fast day.
15	50	5	1100	0	0	—	—	
16 to 20	do	—	—	0	0	—	112	
20	do	—	—	0	0	152	—	
21	30	2	—	0	0	—	—	Fast day.
22 to 27	50	5	1000	0	0	—	—	
27	do	—	—	0	0	131	—	
28	40	10	—	0	0	—	—	Fast day.
29 & 30	60	10	1000	0	0	—	—	
31	do	—	—	0	0	104	110	
September								
1 to 10	50	5	1000	0	0	93	110	
11	40	10	—	0	0	84	—	Fast day.
12 to 17	55	10	1100	0	0	—	—	
17	do	—	—	0	0	90	110	
18	50	10	—	0	0	84	110	Fast day.
19 & 20	60	15	1200	0	0	—	—	
21 to 24	60	15	1300	0	0	—	108	
24	do	—	—	0	0	157	—	
25	30	1	—	0	0	—	—	Fast day.
26	55	10	1100	0	0	—	106	
27	do	—	—	0	0	104	—	
28 & 29	do	—	—	0	0	—	103	
30	do	—	—	0	0	154	102	
October								
1	55	10	1100	0	0	—	—	
2	3	15	—	0	0	—	102	Fast day.
3	55	10	1100	0	0	—	—	
4	do	—	—	0	0	153	—	
5 & 6	do	—	—	0	0	—	—	
7	do	—	—	0	0	—	—	
8	do	—	—	0	0	139	—	
9	do	—	—	0	0	—	103	
10	3	10	—	0	0	—	—	Fast day.
11	55	10	1100	0	0	127	—	
12 to 15	do	—	—	0	0	—	—	
15	do	—	—	0	0	139	105	
16	1	10	—	0	0	100	104	Fast day.

TABLE I. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Oct.—Con.								
17	40	5	200	0	0	—	—	
18	55	10	1100	0	0	93	104	
19	do	—	—	0	0	—	—	
20	do	—	—	0	0	157	—	
21 & 22	do	—	—	0	0	—	107	
23	2	10	—	0	0	—	—	Fast day.
24	40	5	2304	0	0	—	104	
25	40	5	2250	0	0	159	—	
26	40	5	2250	0	0	214	104	Heavy lipemia.
27	40	5	2250	0	0	264	101	Heavy lipemia.
28	58	15	522	0	0	230	100	Heavy lipemia.
29	58	15	522	0	0	—	96	
30	5	10	—	0	0	162	—	Fast day.
31	58	15	522	0	0	—	98	
November								
1 to 7	55	10	1100	0	0	—	98	
7	do	—	—	0	0	79	100	
8 to 11	do	—	—	0	0	—	102	
11	do	—	—	0	0	125	—	
12	do	—	—	0	0	—	—	
13	40	10	—	0	0	—	106	Fast day.
14 to 19	55	10	1100	0	0	100	—	
19	do	—	—	0	0	—	109	100 c.c. alcohol extra.
20	40	5	—	0	0	—	—	120 c.c. alcohol extra.
21	55	10	1100	0	0	—	105	120 c.c. alcohol extra.
22	do	—	—	0	0	178	—	120 c.c. alcohol extra.
23	do	—	—	0	0	—	107	120 c.c. alcohol extra.
24	do	—	—	0	0	—	—	120 c.c. alcohol extra.
25	do	—	—	0	0	260	—	120 c.c. alcohol extra.
26	do	—	—	0	0	—	—	120 c.c. alcohol extra.
27	40	5	—	0	0	214	115	120 c.c. alcohol extra.
28	55	10	1100	0	0	—	—	120 c.c. alcohol extra.
29	do	—	—	0	0	147	110	120 c.c. alcohol extra.
30	do	—	—	0	0	182	—	120 c.c. alcohol extra.
December								
1	55	10	1100	0	0	—	—	120 c.c. alcohol extra.
2	do	—	—	0	0	226	—	120 c.c. alcohol extra.
3	do	—	—	0	0	—	100	120 c.c. alcohol extra.
4	40	5	—	0	0	230	—	
5	55	10	1100	0	0	—	—	
6	do	—	—	0	0	199	98	
7	do	—	—	0	0	—	—	
8	—	—	—	0	0	—	98	
9	do	—	—	0	0	242	—	
10	do	—	—	0	0	—	100	
11	40	10	—	0	0	—	—	Fast day.
12	55	10	1100	0	0	—	—	
13	do	—	—	0	0	203	—	
14 to 18	do	—	—	0	0	—	101	
18	30	1	—	0	0	—	—	Fast day.
19	45	5	900	0	0	119	104	
20 & 21	do	—	—	0	0	—	104	
22	do	—	—	0	0	178	—	
23 to 31	35	4	600	0	0	—	104	
31	do	—	—	0	0	100	—	
1922								
January								
1 to 7	45	5	900	0	0	—	105	
7	do	—	—	0	0	107	—	

TABLE I. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Jan.-Con.								
8	30	1	—	0	0	—	—	
9 to 14	50	5	1000	0	0	—	100	
14	do	—	—	0	0	171	—	
15	30	1	—	0	0	—	98	
16	50	5	1000	0	0	—	98	
17	50	5	1000	0	0	142	98	
18 to 21	45	5	900	0	0	—	98	
21	do	—	—	0	0	214	—	
22	30	1	—	0	0	—	—	Fast day.
23 to 28	45	5	900	0	0	101	98	
29	30	2	—	0	0	—	—	Fast day.
30 & 31	50	5	1000	0		—	96	
February					0			
1	50	5	1000	0		79	—	Weekly fast days omitted during the month of February.
					0			
2 to 11	50	5	1000	0	0	—	100	
11	do	—	—	0	0	100	—	
12 to 18	do	—	—	0	0	—	101	
18	do	—	—	0	0	104	—	
19 to 25	50	5	1100	0	0	—	100	
25	do	—	—	0	0	—	—	
26 & 27	do	—	—	0	0	—	100	
28	do	—	—	0		139	—	
March					0			
1 to 7	50	5	1100	0	0	—	100	
7	do	—	—	0	0	178	—	
8	30	1	—	0	0	—	—	Fast day.
9 to 14	50	5	1100	0	0	—	100	
14	do	—	—	0	0	145	—	
15	30	1	—	0	0	—	100	Fast day.
16 to 25	50	5	1100	0	0	123	100	
26	30	1	—	0	0	—	101	Fast day.
27 to 31	50	5	1100	0	0	—	100	
31	do	—	—	0		121	100	
April					0			
1 to 8	50	5	1100	0	0	—	101	
8	do	—	—	0	0	101	—	
9 to 14	50	5	1100	0	0	—	100	
14	do	—	—	0	0	97	100	
15 to 19	50	10	1100	0	0	—	100	

TABLE II.
Case No. 24.

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reaction in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries						
1919									
August									
4	fast	day	—	heavy	faint	—	—	—	Admitted
5	fast	day	—	heavy	heavy	349	—	93	
6	fast	day	—	slight	heavy	—	—	—	
7	60	—	307	slight	faint	246	27	90	
8	60	—	260	faint	faint	—	—	—	
9	60	—	370	faint	faint	—	—	—	
10	fast	day	—	faint	faint	—	—	91	
11	fast	day	—	0	faint	—	—	—	
12	20	—	84	0	faint	—	—	89	
13 to 17	30	—	135	0	faint	—	—	—	
17	fast	day	—	0	0	—	—	89	
18	30	—	218	0	faint	—	—	89	
19 to 24	40	—	300	0	0	—	—	—	
24	fast	day	—	0	faint	—	—	88	
25	50	—	500	0	faint	100	37	—	
26 to 31	50	—	—	0	faint	—	—	—	
31	fast	day	—	0	faint	—	—	86	
September									
1	60	—	800	0	faint	110	—	85	Fast day.
2 to 7	60	—	—	0	faint	—	—	—	
7	fast	day	—	0	faint	—	—	88	
8	60	5	1000	0	faint	174	39	—	
9	60	—	—	0	faint	150	37	89	
10 to 14	60	—	—	0	faint	—	—	90	
14	fast	day	—	0	faint	—	—	—	
15 to 18	60	—	1000	0	faint	—	—	88	
18 to 20	30	—	600	0	faint	—	—	88	
20	50	—	800	0	faint	200	—	89	
21	fast	day	—	0	faint	—	—	—	
22	50	—	800	0	faint	95	—	—	
23 to 27	—	—	—	0	faint	—	—	88	
27	—	—	—	0	faint	100	—	—	
28	10	—	—	0	faint	—	—	—	
29	50	—	1000	0	faint	68	—	—	
30	—	—	—	0	faint	—	—	—	
October									
1 to 5	50	—	1000	0	faint	—	—	86	Fast day.
5	fast	day	—	0	faint	—	—	—	
6 to 13	50	—	800	0	faint	—	—	—	
13	50	—	800	0	faint	40	54	80	
14 & 15	60	5	1000	0	faint	—	—	—	
16	60	20	1200	0	faint	71	52	74	
17	—	20	—	0	faint	211	—	73	
18	—	20	—	0	faint	—	—	—	
19	—	—	—	—	—	—	—	—	
20	50	70	1230	0	faint	50	92	77	
21	60	5	1200	0	faint	250	129	—	
22	60	5	1400	0	faint	167	143	83	
23 & 24	—	5	—	0	faint	—	—	85	
25	—	5	—	0	faint	349	182	86	
26	60	10	1500	0	faint	—	—	—	
27	40	5	1000	0	faint	300	200	—	
28 to 30	—	5	—	0	faint	—	—	80	

TABLE II. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reac- tion in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries						
Oct.-Con.									
31	—	5	—	0	faint	283	—	84	
November									
1	40	5	1000	0	faint	283	234	—	
2	10	14	300	0	faint	—	—	—	
3	40	5	1000	0	faint	151	221	83	
4	—	5	—	0	faint	256	207	—	
5	—	5	—	0	faint	—	219	—	
6	—	5	—	0	faint	222	206	—	
7 & 8	—	5	—	0	faint	—	—	—	
9	—	8	—	0	faint	—	—	90	Fast day.
10	40	5	1000	0	faint	—	—	—	R.B.C. 1,750,000.
11	—	5	—	0	faint	—	—	91	R.B.C. 1,450,000.
12	—	5	—	0	faint	—	—	—	R.B.C. 1,540,000.
13 to 17	—	5	—	0	faint	—	—	—	
17	—	5	—	0	faint	138	242	—	
18	40	8	900	0	faint	—	—	—	R.B.C. 1,400,000.
19 to 30	40	5	1000	0	faint	—	—	90	
December									
1	40	5	1000	0	faint	230	158	89	R.B.C. 1,760,000.
2 to 7	—	5	—	0	faint	—	—	—	
7	30	—	—	0	faint	—	—	—	Fast day.
8 to 14	40	5	1000	0	0	—	—	89	
14	—	5	—	0	faint	140	118	—	
15 to 28	40	5	1000	0	0	—	—	88	
28	20	3	500	faint	0	—	—	—	Fast day.
29 to 30	40	5	1000	faint	0	—	—	—	
31	—	5	—	faint	0	241	—	88	
1920									
January									
1 to 4	35	6	1000	0	0	—	—	87	
4	30	—	192	0	0	—	—	87	Fast day.
5	40	5	1035	0	0	—	—	—	
6	40	—	—	0	0	206	45	—	
7 & 8	40	5	680	0	0	—	—	—	
9	35	5	1000	0	0	—	—	87	
10 & 11	40	6	1100	0	0	—	—	—	
12	40	5	1000	0	0	140	35	87	
13 to 18	40	5	1100	0	0	—	—	87	
18	15	—	—	0	0	—	—	—	Fast day.
19	40	5	900	0	0	—	—	—	
20	—	5	—	0	0	205	27	88	
21 & 22	40	5	1000	0	0	—	—	—	
23	—	5	—	0	0	123	27	—	
24 to 27	—	5	—	0	0	—	—	—	
27	—	—	—	0	0	184	—	—	
28 to 31	40	6	1000	0	0	—	—	—	
February									
1	20	—	—	0	0	—	—	—	Fast day.
2	40	5	1000	0	0	—	—	—	
3	—	5	—	0	0	168	51	82	
4 to 8	—	5	—	0	0	—	—	82	
8	20	—	140	0	0	—	—	81	
9	40	5	1000	0	0	—	—	—	
10	40	5	1000	0	0	156	22	—	
11 to 15	40	—	—	0	0	—	—	—	
15	20	—	90	0	0	—	—	82	
16	40	5	1000	0	0	—	—	—	
17	40	—	—	0	0	146	—	—	
18 & 19	40	—	—	0	0	—	—	—	

TABLE II. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reaction in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries						
Feb.-Con.									
20	40	—	—	0	0	156	—	81	R.B.C. 4,000,000.
21 to 24	40	—	—	0	0	—	—	—	
24	—	—	—	0	0	117	60	—	
25	50	5	1000	0	0	—	—	—	
26 to 29	50	—	—	0	0	—	—	—	Fast day.
29	20	—	—	0	0	—	—	82	
March									
1	50	5	1000	0	0	—	—	80	
2	—	5	—	0	0	122	124	—	Fast day.
3 to 9	—	5	—	0	0	—	—	—	
9	—	5	—	0	0	209	48	—	
10 & 11	—	5	—	0	0	—	—	—	
12	—	5	—	0	0	173	—	77	Fast day.
13	—	5	—	0	0	—	—	—	
14	20	—	134	0	0	—	—	—	
15	50	5	1000	0	0	—	—	76	
16	50	—	—	0	0	157	78	75	R.B.C. 4,320,000.
17 to 21	40	5	1000	0	0	—	—	74	
21 to 26	20	—	—	0	0	—	—	—	
22 to 26	40	3	1000	0	0	—	—	75	
26	—	3	—	0	0	136	68	—	Fast day.
27	—	3	—	0	0	—	—	—	
28	20	—	—	0	0	—	—	—	
29	40	3	1000	0	0	—	—	—	
30	—	3	—	0	0	139	80	76	Fast day.
31	—	3	—	0	0	—	—	—	
April									
1 & 2	40	3	1000	0	0	—	—	77	
3	—	3	—	0	0	147	—	—	Fast day.
4	20	—	—	0	0	—	—	77	
5	40	3	1000	0	0	120	58	77	
12	—	3	—	0	0	101	—	—	
19	—	3	—	0	0	112	78	77	Fast day.
29	—	3	—	0	0	139	66	77	
May									
1	40	3	1000	0	0	155	—	78	
									Regular fast day once each week during May of 30 grams protein.
17	—	3	—	0	0	161	66	—	Fast day.
13	—	3	—	0	0	130	80	79	
31	—	3	—	0	0	208	42	—	
June									
1 to 15	40	3	1000	0	0	—	—	—	Temporarily dis- charged.
15	—	3	—	heavy	faint	—	—	—	
16	40	3	700	faint	0	288	86	79	
17	—	3	—	faint	faint	—	—	—	
18	10	3	—	faint	—	—	—	—	Heavy lipemia.
19	40	3	700	faint	0	210	—	82	
20	10	—	—	faint	faint	—	—	—	
21	40	3	700	faint	faint	—	—	79	
22	—	3	—	faint	faint	151	—	—	Heavy lipemia.
23	10	—	—	faint	faint	—	—	—	
24	40	3	700	faint	0	166	—	80	
25	—	3	—	faint	faint	258	—	—	
26	30	—	291	faint	0	—	—	—	Heavy lipemia.
27 & 28	10	—	110	faint	0	—	—	80	
29	30	—	—	0	0	116	—	—	

TABLE II. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reac- tion in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries						
June-Con.									
30	40	—	500	0	0	—	—	78	
July									
1 to 6	40	1	500	0	0	—	—	77	
6 to 11	—	1	—	0	0	135	96	—	
12	20	—	—	0	0	—	—	—	Fast day.
13	40	1	800	0	0	116	90	—	
14 to 20	—	1	—	0	0	—	—	80	
20 to 23	—	1	—	0	0	138	—	—	
21 to 23	—	1	—	0	0	—	—	—	
23	—	1	—	0	0	161	120	—	Lipemia heavy.
24	10	—	—	0	0	—	—	—	Fast day.
25 to 28	40	1	800	0	0	—	—	81	
28	10	—	—	0	0	—	—	—	Fast day.
29	40	1	800	0	0	99	68	—	
30 & 31	40	—	—	0	0	—	—	—	
August									
1	—	15	—	0	0	—	—	80	Fast day.
2	40	1	800	0	0	72	—	—	Moderate lipemia.
3 to 6	40	—	—	0	0	—	—	—	
6	40	—	—	0	0	100	—	—	Heavy lipemia.
7	40	1	800	0	0	—	—	—	
8	—	20	—	0	0	—	—	—	Fast day.
9	40	1	800	0	0	80	—	—	Slight lipemia.
10 to 13	40	3	800	0	0	—	—	81	
13	—	3	—	0	0	100	—	—	
14	—	3	—	0	0	—	—	—	
15	—	20	—	0	0	80	—	—	Fast day.
16	40	4	800	0	0	81	—	—	
17 to 21	45	4	800	0	0	—	—	—	
21	45	—	—	0	0	107	—	80	Faint lipemia.
22	20	—	—	0	0	—	—	—	Fast day.
23 to 28	45S	4	800	0	0	—	—	—	30 c.c. whisky daily extra.
28	45	—	—	0	0	97	—	—	30 c.c. whisky daily extra.
29	—	20	—	0	0	—	—	77	Fast day. 30 c.c. whisky daily extra.
30 & 31	45	4	800	0	0	—	—	—	30 c.c. whisky daily extra.
September									
1 & 2	45	4	800	0	0	—	—	76	30 c.c. whisky daily extra.
3	45	4	800	0	0	108	123	—	
4 to 10	45	4	850	0	0	—	—	—	
10	45	—	—	0	0	103	76	75	Moderate lipemia.
11	45	—	—	0	0	—	—	—	
12	—	20	—	0	0	—	—	—	
13 to 24	45	5	850	0	0	—	—	—	
24	45	—	—	0	0	105	92	—	Faint lipemia.
25	50	5	850	0	0	—	—	75	
26	25	25	132	0	0	—	—	—	Fast day.
26 to 30	50	5	850	0	0	—	—	77	
October									
1	50	5	850	0	0	113	—	77	
2 to 8	50	10	900	0	0	—	—	—	
8	50	10	—	0	0	96	104	—	
9	—	10	1000	0	0	—	—	—	
10	—	25	133	0	0	—	—	78	Fast day.

TABLE II. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reaction in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries						
Oct.-Con.									
11 to 16	50	10	1000	0	0	—	—	—	
16	50	—	—	0	0	123	110	—	
17	—	25	133	0	0	—	—	—	
18 to 23	50	10	1000	0	0	—	—	—	
23	50	—	—	0	0	109	116	77	Faint lipemia.
24 to 29	50	5	1000	0	0	—	—	—	
29	50	—	—	0	0	151	—	—	Slight lipemia.
30	50	—	—	0	0	—	—	—	
31	—	25	—	0	0	—	—	—	Fast day.
November									
1	50	5	1000	0	0	—	—	79	
2	50	—	—	0	0	138	72	—	Faint lipemia.
3 & 4	50	5	900	0	0	—	—	—	
5	—	5	—	0	0	161	91	—	
6 to 9	40	2	900	0	0	—	—	—	
9	—	2	—	0	0	181	78	—	
10 to 16	45	2	800	0	0	—	—	79	
16	—	2	—	0	0	116	92	79	
17	—	25	—	0	0	—	—	—	Fast day.
18 to 28	45	4	800	0	0	—	—	—	
28	—	20	—	0	0	—	—	—	
29 & 30	45	4	800	0	0	—	—	79	
December									
1	45	2	800	0	0	134	92	—	Lipemia faint.
2	—	2	—	0	0	123	60	—	Faint lipemia.
3	—	2	—	0	0	121	—	79	Moderate lipemia
4	—	2	—	0	0	—	—	—	
5	30	1	145	0	0	—	—	—	Fast day.
6	45	4	800	0	0	—	—	—	
7	—	4	—	0	0	115	96	—	Slight lipemia.
8 & 9	—	4	—	0	0	—	—	—	
10	—	4	—	0	0	138	24	80	Moderate lipemia.
11	—	4	—	0	0	—	—	—	
12	—	19	90	0	0	—	—	—	Fast day.
13	50	5	850	0	0	—	—	—	
14	—	5	—	0	0	117	—	—	
15 to 22	—	5	—	0	0	—	—	—	
22	30	1	—	0	0	—	—	—	Fast day.
23 to 31	50	5	850	0	0	—	—	80	
31	—	5	—	0	0	119	—	—	
1921									
January									
1 to 8	50	5	900	0	0	—	—	79	
8	30	—	—	0	0	—	—	—	Fast day.
9 to 16	50	5	900	0	0	131	—	—	
16	30	1	—	0	0	—	—	78	Fast day.
17 to 24	50	5	900	0	0	122	—	—	
25	30	1	—	0	0	—	—	77	Fast day.
26 to 31	50	5	900	0	0	—	—	—	
31	—	5	—	0	0	110	—	—	
February									
1 to 7	50	10	950	0	0	—	—	—	
7	30	1	—	0	0	114	—	77	Fast day.
8 to 15	50	10	950	0	0	—	—	—	
15	25	10	—	0	0	—	—	78	Fast day.
16 to 23	50	10	950	0	0	—	—	—	
23	20	10	—	0	0	—	—	—	Fast day.
24 to 28	50	10	950	0	0	—	—	77	
28	50	—	—	0	0	—	—	—	

TABLE II. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reaction in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries						
March									
1 to 6	50	10	1000	0	0	—	—	77	
6	35	5	—	0	0	118	—	—	Fast day.
7 to 18	50	10	1000	0	0	—	—	—	
18	20	10	—	0	0	129	—	77	Fast day.
19 to 28	50	10	1000	0	0	—	—	—	
28	25	5	—	0	0	131	—	77	Fast day.
29	50	10	1000	0	0	—	—	—	
30	50	—	—	0	0	—	—	77	
31	50	—	—	0	0	116	—	—	
April									
1 to 6	50	10	1000	0	0	—	—	—	
6	20	5	—	0	0	111	—	76	
7 to 10	50	10	1000	0	0	—	—	—	
10	50	10	1000	0	0	123	—	76	
11 to 17	50	—	—	0	0	—	—	—	
12	30	5	—	0	0	—	—	76	Fast day.
13 to 20	50	10	1000	0	0	—	—	—	
20	50	—	—	0	0	141	—	75	
21	25	5	—	0	0	—	—	—	Fast day.
22 to 28	50	10	1000	0	0	—	—	76	
28	50	—	—	0	0	111	—	—	
29	25	5	—	0	0	—	—	76	Fast day.
30	50	10	1000	0	0	—	—	75	
May									
1 to 3	50	10	1000	0	0	—	—	—	
3	50	—	—	0	0	99	60	78	
4 to 15	50	10	1000	0	0	—	—	—	
15	25	4	—	0	0	—	—	—	Fast day.
16	55	10	1000	0	0	135	40	82	
17 to 21	—	10	—	0	0	—	—	83	
21	55	—	—	0	0	136	—	—	
22	20	10	—	0	0	—	—	—	Fast day.
23 to 28	55	10	1000	0	0	—	—	—	
28	—	10	—	0	0	117	64	85	
29	5	15	—	0	0	—	—	—	Fast day.
29 to 31	55	10	1000	0	0	—	—	—	
31	55	—	—	0	0	107	40	86	Moderate lipemia.
June									
1 to 4	50	15	1000	0	0	—	—	—	
4	50	—	—	0	0	123	40	83	Moderate lipemia.
5	25	10	—	0	0	—	—	—	
6 to 11	50	15	1000	0	0	—	—	—	
11	50	—	—	0	0	146	80	—	Moderate lipemia.
12	10	20	—	0	0	—	—	—	Fast day.
13 to 18	50	15	1000	0	0	—	—	85	
18	50	—	—	0	0	101	52	—	Faint lipemia.
19 to 25	50	20	1000	0	0	—	—	—	
25	—	20	—	0	0	100	120	84	
26	15	15	—	0	0	—	—	81	Fast day.
26 to 30	50	25	1100	0	0	—	—	—	
30	50	—	—	0	0	115	42	81	Slight lipemia.
July									
1 to 5	55	25	1100	0	0	—	—	83	
5	55	—	—	0	0	107	—	—	Slight lipemia.
6 to 8	55	30	1100	0	0	—	—	—	
8	55	—	—	0	0	125	58	—	Moderate lipemia.
9	55	20	900	0	0	—	—	—	
10	30	15	—	0	0	—	—	83	Fast day.
11 to 15	55	20	1000	0	0	—	—	—	

TABLE II. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reac- tion in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries						
July-Con.									
16	60	30	1100	0	0	113	68	83	
17	—	25	—	0	0	—	—	80	Fast day.
18 to 23	50	25	1200	0	0	—	—	78	
23	50	—	—	0	0	116	40	75	Moderate lipemia.
24	20	15	—	0	0	—	—	—	Fast day.
25 to 30	50	25	1200	0	0	—	—	80	
30	50	—	—	0	0	154	74	—	Heavy lipemia.
31	15	15	—	0	0	—	—	—	
August									
1	50	25	1200	0	0	—	—	81	
2	—	25	—	0	0	174	32	—	Moderate lipemia.
3 to 5	50	25	1200	0	0	—	—	—	
5	—	—	—	0	0	140	74	—	
6	50	—	—	0	0	—	—	—	
7	30	5	—	0	0	—	—	78	Fast day.
8 to 12	50	25	1200	0	0	—	—	77	
12	—	25	—	0	0	175	44	—	Heavy lipemia.
13	50	15	900	0	0	180	—	—	Heavy lipemia.
14	25	10	—	0	0	—	—	—	Fast day.
15 to 19	55	15	1000	0	0	—	—	78	
20	55	—	—	0	0	104	—	—	Heavy lipemia.
21	30	25	—	0	0	—	—	78	Fast day.
22 to 27	55	25	1100	0	0	—	—	—	
27	55	—	—	0	0	107	40	—	
28	30	25	—	0	0	—	—	78	
29	55	25	1100	0	0	—	—	—	
30	—	25	—	0	0	105	—	77	
31	—	25	—	0	0	—	—	—	
September									
1 to 9	55	30	1200	0	0	—	—	—	
9	55	—	—	0	0	122	—	80	
10	60	30	1300	0	0	—	—	—	
11	30	25	—	0	0	—	—	80	Fast day.
12	60	35	1300	0	0	—	—	—	
13	—	35	—	0	0	178	34	—	
14 & 15	60	25	1300	0	0	—	—	—	
16	—	25	—	0	0	260	42	82	
17	40	10	—	0	0	200	—	—	
18 to 23	60	15	—	0	0	—	—	81	
23	60	—	—	0	0	189	—	—	
24 & 26	45	5	500	0	0	—	—	—	
27	45	—	—	0	0	131	—	—	
28 & 29	50	10	1000	0	0	—	—	—	
30	50	—	—	0	0	136	—	83	
October									
1	4	25	—	0	0	—	—	—	Fast day.
2 to 7	50	15	1000	0	0	—	—	82	
7	50	—	—	0	0	129	—	—	
8	3	10	—	0	0	—	—	83	Fast day.
9 to 15	50	15	1000	0	0	—	—	—	
15	50	—	—	0	0	133	—	—	
16	—	10	—	0	0	—	—	—	Fast day.
17 to 22	50	15	1000	0	0	—	—	80	
22	50	—	—	0	0	137	—	—	
23	—	10	—	0	0	—	—	78	
24	40	5	1890	0	0	—	—	76	
25	—	5	—	0	0	242	—	—	Moderate lipemia.
26	—	5	—	0	0	300	—	—	Moderate lipemia.
27	60	10	496	0	0	375	—	—	Moderate lipemia.

TABLE II. (Continued)

Date	DIET			Quali- tative Dextrose in Urine	Nitro- prusside Reac- tion in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries						
Oct.—Con.									
28	—	10	—	0	0	306	—	—	Moderate lipemia.
29	—	10	—	0	0	—	—	77	
30	—	10	—	0	0	184	—	—	
31	60	10	496	0	0	173	—	—	
November									
1	50	15	1000	0	0	102	102	—	
2 & 3	—	15	—	0	0	—	—	77	
4	—	15	—	0	0	121	—	—	
5	—	15	—	0	0	—	—	76	
6	—	10	—	0	0	—	—	—	
7	50	15	1000	0	0	—	—	79	
8	—	15	—	0	0	93	—	—	
9 & 10	—	15	—	0	0	—	—	—	
11	—	15	—	0	0	152	—	—	
12	—	15	—	0	0	—	—	81	
13	40	5	—	0	0	—	—	—	Fast day.
14	50	15	1000	0	0	—	—	—	
15	—	15	—	0	0	116	—	83	
16	—	15	—	0	0	—	—	—	
17	50	15	1700	0	0	—	—	—	Including 700 c.c. of alcohol.
18	50	—	—	0	0	171	—	—	Including 700 c.c. of alcohol.
19	50	—	—	0	0	—	—	81	Including 700 c.c. of alcohol.
20	50	15	1840	0	0	—	—	—	Including 700 c.c. of alcohol.
21	50	—	—	0	0	—	—	—	Including 700 c.c. of alcohol.
22	50	—	—	0	0	214	—	—	Lipemia.
23	50	—	—	0	0	—	—	—	Lipemia.
24	50	—	—	0	0	—	—	82	Lipemia.
25	—	—	—	0	0	270	—	—	Lipemia.
26	50	—	—	0	0	285	—	—	Lipemia heavy.
27	40	5	—	faint	0	—	—	—	Fast day.
28	50	15	1000	faint	0	230	—	82	
29	—	15	—	0	0	—	—	83	
30	—	15	—	0	0	319	46	81	
December									
1	—	15	—	faint	0	—	—	—	
2	—	15	—	faint	0	312	46	78	
3	—	15	—	faint	0	—	—	—	
4	40	5	—	0	0	—	—	—	
5	50	15	1000	0	0	187	—	78	
6 to 11	—	15	—	0	0	—	—	—	
11	40	5	—	0	0	295	—	79	Heavy lipemia.
12	25	5	—	0	0	—	—	—	
13	44	10	—	0	0	150	84	—	
14	30	5	—	0	0	—	—	—	
15	35	5	640	0	0	—	—	—	
16	40	5	1000	0	0	156	—	77	
17	45	5	1000	0	0	—	—	—	
18	40	5	800	0	0	—	—	—	
19	55	10	1000	0	0	—	—	—	
20	—	10	—	0	0	246	78	—	Faint lipemia.
21	30	2	—	0	0	—	—	—	
22	37	4	—	0	0	173	80	77	
23	30	3	350	0	0	143	80	—	

TABLE II. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reac- tion in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries						
Dec.-Con.									
24	30	3	329	0	0	143	—	—	
25	35	5	600	0	0	—	—	—	
26	35	5	600	0	0	184	92	—	
27	35	3	550	0	0	—	—	—	
28	35	3	500	0	0	119	82	77	
29	45	5	650	0	0	—	—	—	
30	45	5	650	0	0	—	—	77	
31	—	5	—	0	0	—	—	—	
1922									
January									
1	45	5	650	0	0	129	—	—	
2 & 3	—	5	—	0	0	—	—	—	
4	45	5	800	0	0	107	36	76	
5	—	5	—	0	0	—	—	—	
6	45	5	900	0	0	—	—	—	
7	—	5	—	0	0	142	—	—	Faint lipemia.
8	25	2	—	0	0	—	—	—	Fast day.
9	45	5	900	0	0	—	—	79	
10	—	5	—	0	0	135	—	—	
11 & 12	—	5	—	0	0	—	—	81	
13	—	5	—	0	0	214	—	—	Heavy lipemia.
14	20	2	—	0	0	—	—	—	Fast day.
15	20	—	—	0	0	—	—	—	Fast day.
16	45	5	900	0	0	—	—	—	
17	—	5	—	0	0	154	72	—	
18 & 19	45	5	700	0	0	—	—	80	
20	—	5	—	0	0	182	—	—	
21	—	5	—	0	0	—	—	—	
22	20	2	—	0	0	—	—	—	
23	46	6	—	0	0	106	—	—	
24 to 28	50	10	800	0	0	—	—	—	
28	—	10	—	0	0	126	—	—	
29	40	2	400	0	0	—	—	—	Fast day.
30	50	10	800	0	0	—	—	86	
31	—	10	—	0	0	84	—	—	
February									
1 to 4	55	10	900	0	0	—	—	84	
4	—	10	—	0	0	118	—	84	
5 to 10	—	10	—	0	0	—	—	—	
10	—	10	—	0	0	126	—	—	
11	35	5	500	0	0	—	—	—	Fast day.
12 to 19	55	15	900	0	0	—	—	—	
19	—	15	—	0	0	117	78	81	
20	35	5	500	0	0	—	—	—	
21 to 26	55	15	1000	0	0	—	—	—	
26	—	15	—	0	0	118	86	80	
27	35	5	500	0	0	—	—	81	
28	55	17	1000	0	0	—	—	—	
March									
1	55	17	1000	0	0	—	—	79	
2	—	17	—	0	0	—	—	—	
3	—	17	—	0	0	275	92	78	
4	—	17	—	0	0	—	—	—	
5	20	10	—	0	0	—	—	81	Fast day.
6	40	5	700	0	0	—	—	—	
7	—	5	—	0	0	200	—	—	
8	—	5	—	0	0	—	—	81	
9	—	5	—	0	0	192	64	—	
10	—	5	—	0	0	—	—	—	

TABLE II. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reaction in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries						
Mar.-Con.									
11	—	5	—	0	0	139	—	—	
12	—	5	—	0	0	—	—	80	
13	45	10	900	0	0	107	—	—	
14 & 15	—	10	—	0	0	—	—	—	
16	—	10	—	0	0	142	—	—	
17 & 18	—	10	—	0	0	—	—	—	
19	25	5	—	0	0	—	—	—	
20	45	10	900	0	0	—	—	—	
21	—	10	—	0	0	156	62	—	
22 to 25	—	10	—	0	0	—	—	—	
25	—	10	—	0	0	137	—	—	
26	35	5	500	0	0	—	—	81	Fast day.
27	45	10	900	0	0	—	—	—	
28	45	10	900	0	0	—	—	—	
29	—	10	—	0	0	—	—	81	
30	—	10	—	0	0	107	—	—	

TABLE III.
Case No. 41.

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reac- tion in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Wgt. Lbs.	Blood Pressure	Remarks
	Pro- tein Gms.	CH. Gms.	Total Calo- ries							
1919 August 17	4	9	266	slight	0	—	—	—	214/160	Admitted. Heavy albumin. Gra- nular casts. Salt free diet.
18	2	10	—	0	0	176	134	87	—	CO ₂ 61.5 vol. %. Salt free diet.
19	3	152	1373	0	0	—	—	—	—	Phenolphthalein test 5.0%. Salt free diet.
20	fast	day	—	0	0	—	—	—	—	Salt free diet.
21	1	50	1027	0	0	—	—	—	—	Wassermann test negative. Salt free diet.
22 to 25	1	50	1027	0	0	208	131	82	—	Salt free diet.
26	2	50	981	0	0	—	—	—	—	Salt free diet.
27	2	50	1505	0	0	—	—	86	—	Salt free diet.
28	2	50	1505	0	0	—	72	—	—	Salt free diet.
29	2	50	1505	0	0	—	—	87	208/156	Albumin 2 plus. Salt free diet.
30	2	50	216	0	0	192	48	—	202/140	CO ₂ 52.2 vol. %. Salt free diet.
31 September	fast	day	—	0	0	—	—	85	195/140	Salt free diet.
1	2	50	1150	0	0	134	35	—	186/132	Salt free diet.
2	2	50	1150	0	0	—	—	83	172/135	Salt free diet.
3 & 4	2	50	1500	0	0	—	—	—	—	Albumin 3 plus. Salt free diet.
5	2	50	1500	0	0	156	45	—	172/140	Salt free diet.
6 & 7	2	50	1500	0	0	—	—	81	158/120	Salt free diet.
8	3	20	104	0	0	—	—	—	148/115	Fast day. Salt free diet.
9	30	30	1200	0	0	181	63	—	152/115	Salt free diet.
10 to 14	30	30	1200	0	0	—	—	78	155/110	Salt free diet.
14	fast	day	—	0	0	—	—	78	150/120	Salt free diet.
15	30	30	1200	0	0	—	106	—	156/110	Salt free diet.
16	30	30	1200	0	0	181	117	80	158/125	Salt free diet.
17	30	30	1200	0	0	—	—	80	156/185	Salt free diet.
18	30	30	1200	0	0	144	115	—	158/108	Salt free diet.
19	30	30	1200	0	0	179	90	78	—	Salt free diet.
20	fast	day	—	0	0	—	—	—	—	—
21	30	30	1203	0	0	—	88	82	159/106	Salt free diet.
22 & 23	30	30	1203	0	0	—	—	—	—	—
24	30	30	1203	0	0	174	72	—	162/114	Salt free diet.
25 & 26	30	30	1203	0	0	—	—	82	158/117	Salt free diet.
27	30	30	1203	0	0	123	59	81	—	Salt free diet.
28	30	30	1203	0	0	—	—	82	150/110	10 gr. salt daily
29	30	30	1203	0	0	—	—	82	—	10 gr. salt daily.
30	30	30	1203	0	0	—	—	83	159/108	10 gr. salt daily.
October 1	30	30	1203	0	0	—	—	84	168/110	10 gr. salt daily.
2	30	30	1203	0	0	—	—	87	—	10 gr. salt daily.
3	30	30	1203	0	0	—	—	88	—	10 gr. salt daily.

TABLE III. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reaction in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Wgt. Lbs.	Blood Pressure	Remarks
	Protein Gms.	CH. Gms.	Total Calo- ries							
Oct.—Con.										
4	30	30	1203	0	0	134	47	90	—	Phenolphthalein test 27.0%.
5	fast	day	—	0	0	—	—	90	—	10 gm. salt daily.
6	30	30	1200	0	0	—	—	88	—	10 gm. salt daily.
7	30	30	1200	0	0	158	64	88	148/110	Edema of ankles.
8 to 11	30	30	1200	0	0	—	—	90	160/120	
11	30	30	1200	0	0	134	50	—	140/90	Phenolphthalein test 21.9%.
12	fast	day	—	0	0	—	—	88	162/106	
13	30	30	1200	0	0	105	63	88	150/106	Phenolphthalein test 21.0%. 2 gm. salt daily added to diet.
14 to 22	30	30	1200	0	0	—	—	—	156/1104	2 gm. NaCl daily.
22	30	30	1200	0	0	145	59	89	—	do.
23 to 26	30	30	1200	0	0	—	—	87	—	do.
26	30	30	1200	0	0	118	47	87	—	do.
27 to 31	30	30	1200	0	0	—	—	88	—	do.
November										
1	30	30	1200	0	0	92	55	—	158/120	do.
2 to 6	30	30	1200	0	0	—	—	90	—	do.
6	30	30	1200	0	0	98	42	90	—	do.
7 to 10	30	30	1200	0	0	—	—	88	—	do.
10	30	30	1200	0	0	190	35	—	160/120	do.
11 to 17	30	30	1200	0	0	—	—	85	—	do.
17	30	30	1200	0	0	142	61	82	—	do.
18 to 24	30	30	1200	0	0	—	—	80	160/110	do.
24	30	40	1299	0	0	123	31	—	150/110	Discharged. Fol- lowing weighed diet at home. 2 gm. NaCl in the diet daily.
December										
13	30	40	1299	0	0	171	72	—	—	Takes weekly fast day of 30 grams protein.
29	30	40	1299	0	0	233	89	—	—	do.
1920										
January										
5	30	40	1299	0	0	180	43	—	180/120	do.
6	30	20	1200	0	0	—	—	—	—	do.
26	30	20	1200	0	0	166	77	—	—	do.
February										
16	40	30	1200	0	0	178	112	—	—	do.
March										
5	40	30	1200	0	0	167	86	—	—	do.
29	40	30	1200	0	0	137	40	—	—	do.
April										
1	35	20	1400	0	0	132	40	—	—	do.
23	35	20	1400	0	0	130	72	—	—	do.
June										
4	35	20	1400	0	0	149	92	—	—	do.
July										
7	35	20	1400	0	0	161	47	—	—	Takes weekly fast day of 30 grams protein.
25	35	20	1400	0	0	—	—	—	—	do.

TABLE III. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reaction in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Wgt. Lbs.	Blood Pressure	Remarks
	Protein Gms.	CH. Gms.	Total Calo- ries							
July—Con.										
26	35	20	1400	0	0	192	132	—	180/130	Readmitted to In- stitute.
27	35	20	1400	0	0	—	—	—	—	
28	fast	day	—	—	—	—	—	—	—	
29	30	10	1200	0	0	—	—	—	—	
30	30	10	1200	0	0	129	—	—	—	
31	30	10	1200	0	0	—	—	—	—	
August										
1	3	15	72	0	0	—	—	—	—	Fast day.
2	30	10	1200	0	0	159	82	—	—	
3 & 4	30	10	1200	0	0	—	—	—	—	
5	30	10	1200	0	0	129	—	—	—	
6	30	10	1200	0	0	138	100	—	—	
7	30	10	1200	0	0	—	—	—	—	Discharged.
September										
14	30	10	1200	0	0	103	—	—	—	Takes weekly fast day of 30 grams protein.
October										
4	30	10	1200	0	0	76	—	—	175/140	
November										
1	40	20	1400	0	0	108	104	—	—	
December										
6	40	20	1400	0	0	170	158	—	178/146	
7 to 10	40	—	—	0	0	—	—	—	—	
11	40	20	1400	0	0	—	—	—	—	
13	40	20	1400	0	0	—	—	—	188/120	
14	30	—	—	0	0	—	—	—	—	
15	35	5	—	0	0	—	—	—	—	
16 to 20	35	15	800	0	0	—	—	—	—	
20	40	20	1400	0	0	231	—	—	—	Infection follow- ing laceration of foot.
25	20	—	94	0	0	—	—	—	—	Readmitted to In- stitute.
26	20	—	94	0	0	—	—	—	—	
27	20	—	143	0	0	152	—	—	—	
28	20	—	151	0	0	131	130	—	—	
29	20	—	151	0	0	133	154	—	—	
30	20	—	151	0	0	—	—	—	—	
31	20	—	151	0	0	118	160	—	—	
1921										
January										
1	30	—	597	0	0	133	150	—	—	
2	30	—	597	0	0	—	—	—	—	
3	30	—	597	0	0	133	147	—	—	Discharged.
4	30	10	700	0	0	—	—	—	—	Weekly fast day of 30 grams pro- tein.
8	30	10	700	0	0	201	160	—	—	
9	30	5	500	0	0	—	—	—	—	
12	35	10	800	0	0	—	—	—	—	
13	35	10	800	0	0	—	—	—	—	
14	35	10	800	0	0	237	142	—	—	
15	35	10	800	0	0	157	—	—	—	
16	35	15	1000	0	0	—	—	87	—	
21	35	15	1000	0	0	142	138	—	—	
28	35	15	900	0	0	—	—	—	—	

TABLE III. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Nitro- prusside Reaction in Urine	Plasma Sugar Mg. per 100 c.c.	Blood Urea Mg. per 100 c.c.	Body Wgt. Lbs.	Blood Pressure	Remarks
	Protein Gms.	CH. Gms.	Total Calo- ries							
February										
4	35	15	900	0	0	145	—	—	—	
5	45	15	1200	0	0	—	—	—	—	
March										
2	45	15	1200	0	0	223	—	80	—	
3	40	20	1100	0	0	—	—	—	—	
April										
2	40	20	1100	0	0	156	—	—	154/110	
11	40	20	1000	0	0	157	—	—	—	
May										
1	50	25	1000	0	0	—	—	—	—	
23	50	25	1000	0	0	210	—	85	—	
June										
1	50	25	1100	0	0	211	—	85	—	
3	35	25	900	0	0	197	—	85	150/120	
7	30	15	500	0	0	155	—	—	—	
8	35	20	700	0	0	143	—	85	—	
9	35	25	900	0	0	198	—	—	—	
19	5	15	180	0	0	—	—	—	—	Readmitted to In- stitute.
20	5	15	180	0	0	—	—	—	—	
21	5	15	180	0	0	117	202	74	—	
22	10	25	400	0	0	—	—	—	—	
23	10	25	400	0	0	168	326	72	—	
24	10	25	400	0	0	117	330	—	—	
25	10	25	400	0	0	—	330	—	—	
26	10	30	600	0	0	—	—	68	—	
27	10	30	600	0	0	156	327	—	—	Died.

TABLE IV.

Case No. 54.

Date	DIET			Qualitative Dextrose in Urine	Qualitative Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
1919 September 28	fast	day	—	heavy	heavy	357	94	CO ₂ 46.2 Blood urea 13.6 Admitted.
29 & 30 October	fast	day	—	faint	heavy	—	94	
1	30	—	194	0	mod.	—	95	CO ₂ 49.4 Blood urea 17.
2 & 3	30	—	196	0	mod.	—	97	
4	50	—	262	0	mod.	195	99	
5	fast	day	—	0	slight	—	—	
6	50	—	231	0	slight	205	99	
7	50	—	259	0	mod.	—	—	
8	50	—	302	0	slight	—	98	
9	50	—	302	0	mod.	—	96	
10 & 11	30	10	218	0	slight	—	—	
12	fast	day	—	0	slight	—	95	
13	30	10	220	0	slight	134	—	Fast day. Blood urea 15 mg.
14 & 15	40	15	499	0	slight	—	93	
16	40	15	499	0	slight	—	92	
17	40	15	499	0	slight	134	92	
18	40	15	499	0	slight	150	—	
19	10	10	80	0	slight	—	91	
20 to 26	40	15	500	0	slight	—	91	
26	—	10	86	0	slight	—	—	
27	40	15	500	0	slight	156	91	
28	40	15	500	0	slight	—	—	
29	40	15	500	0	slight	—	90	
30 & 31	40	15	500	0	slight	—	90	
November 1	40	15	500	0	slight	158	—	Fast day.
2	10	10	102	0	slight	—	90	
3	40	15	500	0	slight	139	90	
4	26	12	340	0	slight	—	91	Blood urea 16.
5	fast	day	—	0	slight	—	—	
6	fast	day	—	0	slight	120	91	
7	40	5	268	0	slight	—	—	
8 to 12	40	5	200	0	faint	—	89	
12	40	5	200	0	slight	152	89	
13	40	5	800	0	slight	184	—	
14 & 15	40	5	800	0	slight	—	90	
16	fast	day	—	0	faint	—	89	
17 to 23	40	5	800	0	slight	—	89	
23	fast	day	—	0	faint	—	—	
24	40	5	800	0	mod.	144	89	
25 to 29	40	5	800	0	slight	—	89	
29	40	5	800	0	faint	184	88	
30	fast	day	—	0	faint	—	89	
December 1 to 5	40	5	800	0	slight	—	88	
5	40	5	800	0	slight	161	86	
6	40	5	800	0	slight	—	87	
7	fast	day	—	0	slight	—	—	
8 to 11	40	5	800	0	slight	—	86	
11	50	5	716	0	slight	162	87	

TABLE IV. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Dec.-Con.								
12 & 13	50	5	716	0	faint	172	—	
14	fast	day	—	0	faint	—	84	
15 & 16	40	5	800	0	faint	—	—	
17	40	5	800	0	faint	113	83	
18	40	5	800	0	faint	127	83	
19	40	5	800	0	faint	113	—	
20	40	5	800	0	faint	142	83	
23	40	5	1000	0	0	—	—	Discharged. Left the city. On weighed diet.
1920								
January	40	5	1000	0	0	—	—	Complete fast days each week.
February	40	5	1000	0	0	—	—	Complete fast days each week.
March	40	5	1000	0	0	—	—	Complete fast days each week.
April 28	40	5	1000	0	0	135	82	No glycosuria on 40 protein, 5 CH and 1000 calories since Dec. 23, 1919. Complete fast days each week.
29	45	5	1050	0	0	135	82	Returned to Institute.
May 5	45	5	1050	0	0	142	—	Complete fast day each week.
24	45	5	1050	0	0	142	—	Complete fast day each week.
June 5	45	5	1050	0	0	133	—	Complete fast day each week.
20	45	5	1050	0	0	128	83	Complete fast day each week.
22	50	5	1050	0	0	118	—	Discharged.
July	50	5	1050	0	0	—	—	Complete fast day each week.
August	50	5	1050	0	0	—	—	Same.
September	50	5	1050	traces	0	—	84	Intermittent glycosuria. Diet reduced to 500 calories with many fast days, but glycosuria appeared
October	—	—	—	traces	—	—	—	In spite of reduced diet and irregular fast days glycosuria appeared intermittently.
November	—	—	—	traces	—	—	—	Continued to have traces of sugar which disappeared on fasting.
29	10	—	—	heavy	faint	—	—	Returned for treatment.
30	10	—	—	heavy	faint	—	—	
December 1	10	—	—	faint	faint	—	—	
2	10	—	—	faint	faint	—	—	

TABLE IV. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Dec.-Con.								
3	10	—	—	0	0	—	—	
4	10	—	—	—	—	—	—	
5	10	—	—	0	0	—	—	
6	—	—	—	0	0	—	—	Complete fast day.
7	10	—	—	0	0	—	—	
8	10	—	—	0	0	—	—	
9	10	—	—	0	0	—	—	
10	10	—	—	0	0	—	—	
11	10	—	—	0	0	—	—	
12	10	—	—	0	0	—	—	
13	—	—	—	0	0	—	—	Complete fast day.
14	10	—	—	0	0	—	—	
15	10	—	—	0	0	—	—	
16	10	—	—	0	0	—	—	
17	10	—	50	0	faint	—	73	
18	30	—	247	0	faint	308	—	
19 & 20	30	—	184	0	0	—	74	
21	30	—	192	0	v. faint	210	—	
22 & 23	30	—	189	0	0	—	74	
24	30	—	180	0	0	195	—	
25	40	5	600	0	0	—	73	
26 & 27	30	—	137	0	0	—	—	
28	30	—	289	0	v. faint	161	—	
29	30	—	228	0	0	159	74	
30	30	—	228	0	0	—	—	
31	30	—	300	0	0	149	73	
1921								
January								
1	30	—	264	0	0	—	—	
2	15	—	74	0	0	—	73	
3	40	—	340	0	0	—	—	
4	40	—	400	0	0	118	72	
5 & 6	40	—	400	0	0	—	72	
7	40	—	400	0	0	139	—	
8 & 9	40	—	400	0	0	—	72	
10	40	—	400	0	0	—	71	
11	40	—	400	0	0	179	—	
12 & 13	40	—	400	0	0	—	71	
14	40	—	400	0	0	121	—	
15 to 18	40	—	450	0	0	—	71	
18	40	—	500	0	0	100	—	
19	40	2	750	0	0	—	—	
20	40	2	750	0	0	—	72	
21	40	2	750	0	0	145	—	
22	40	2	750	0	0	—	71	
23	20	—	—	0	0	—	—	Fast day.
24	40	2	500	0	0	—	72	
25	40	2	700	0	0	152	—	
26 & 27	30	—	550	0	0	—	70	
28	30	—	550	0	0	140	—	
29	30	—	550	0	0	—	70	
30	40	—	—	0	0	—	—	Fast day.
31	30	—	500	0	0	—	70	
February								
1 to 4	30	—	500	0	0	—	71	
4	30	—	500	0	0	139	—	
5	30	—	500	0	0	—	70	
6	30	—	—	0	0	—	—	Fast day.

TABLE IV. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Feb.-Con.								
7	30	—	500	0	0	—	70	
8	30	—	500	0	0	134	—	
9 to 12	30	—	500	0	0	—	72	
12	30	—	500	0	0	136	—	
13	30	—	—	0	0	—	—	Fast day.
14	30	—	500	0	0	—	—	
15	30	—	500	0	0	123	70	
16 & 17	30	—	500	0	0	—	69	
18	35	2	550	0	0	103	—	
19	35	2	550	0	0	—	71	
20	30	—	—	0	0	—	—	Fast day.
21	40	2	600	0	0	—	70	
22	40	2	600	0	0	110	—	
23 & 24	40	2	750	0	0	—	71	
25	40	2	750	0	0	149	71	
26	40	2	750	0	0	—	—	
27	40	2	750	0	0	—	73	
28	40	2	750	0	0	—	—	
March								
1	40	2	750	0	0	145	70	
2	40	2	750	0	0	—	—	
3	35	2	700	0	0	—	70	
4	35	2	700	0	0	110	—	
5 to 8	35	2	700	0	0	—	70	
8	40	2	700	0	0	112	—	
9 & 10	40	2	700	0	0	—	69	
11	40	2	700	0	0	112	71	
12 & 13	40	—	650	0	0	—	70	
14	40	—	650	0	0	135	—	
15	30	—	—	0	0	—	70	Fast day.
16 & 17	40	2	500	0	0	—	70	
18	40	2	650	0	0	111	—	
19	40	2	650	0	0	—	69	
20	40	2	650	0	0	150	—	
21	40	2	650	0	0	—	69	
22	25	1	—	0	0	—	—	Fast day.
23 & 24	40	2	500	0	0	—	68	
25	40	2	500	0	0	111	67	
26	40	2	500	0	0	—	—	
27	30	1	—	0	0	—	68	Fast day.
28	40	2	650	0	0	—	—	
29	40	2	650	0	0	110	—	
30 & 31	40	2	650	0	0	—	68	
April								
1	45	3	700	0	0	113	—	
2	45	3	700	0	0	—	69	
3	30	1	—	0	0	—	—	Fast day.
4 & 5	45	3	700	0	0	—	68	
6 & 7	45	3	700	0	0	—	70	
8	45	3	700	0	0	080	68	
9	45	3	700	0	0	—	—	
10	30	1	—	0	0	—	67	Fast day.
11	50	3	750	0	0	—	—	
12	50	3	750	0	0	138	68	
13 to 16	50	3	750	0	0	—	68	
16	50	3	750	0	0	—	67	
17	30	1	—	0	0	—	—	Fast day.
18 to 22	50	3	900	0	0	—	68	
22	50	3	900	0	0	103	70	

TABLE IV. (Continued)

Date	DIET			Qualitative Dextrose in Urine	Qualitative Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Apr.-Con.								
23	50	3	900	0	0	—	—	
24	30	1	—	0	0	—	69	Fast day.
25 to 28	55	5	1050	0	0	—	66	
28	55	5	1050	0	0	—	69	
29	55	5	1050	0	0	118	—	
30	55	5	1050	0	0	—	68	
1921								
May								
1	30	1	260	0	0	—	68	Fast day.
2 to 6	55	5	1100	0	0	—	—	
6	55	5	1100	0	0	135	68	
7	55	5	1100	0	0	—	68	
8	25	5	220	0	0	—	68	Fast day.
9	55	5	1100	0	0	—	—	
10	55	5	1100	0	0	130	68	
11 & 12	55	5	1100	0	0	—	—	
13	55	5	1000	0	0	123	68	
14	55	5	1000	0	0	—	—	
15	30	1	241	0	0	—	67	Fast day.
16 & 17	55	5	1000	0	0	—	67	
18	55	5	1000	0	0	170	—	
19	55	5	1000	0	0	—	68	
20 & 21	55	5	800	0	0	—	68	
22	25	1	227	0	0	—	69	Fast day.
23	40	5	800	0	0	—	69	
24	40	5	800	0	0	133	—	
25 & 26	35	5	700	0	0	—	66	
27	35	5	700	0	0	123	—	
28	35	5	700	0	0	—	67	
29	25	1	208	0	0	—	—	Fast day.
30 & 31	35	5	700	0	0	—	—	
1921								
June								
1	35	5	700	0	faint	118	68	
2	35	5	700	0	faint	—	67	
3	35	5	700	0	faint	115	—	
4	45	5	900	0	0	—	67	
5 & 6	45	5	900	0	0	—	67	
7	45	5	900	0	0	120	—	
8	30	1	—	0	0	—	—	Fast day.
9	45	5	900	0	0	—	67	
10	45	5	900	0	0	127	—	
11	45	5	900	0	0	—	68	
12	30	0	255	0	0	—	—	
13	45	5	900	0	0	—	—	
14	45	5	900	0	0	150	—	
15 & 16	45	5	900	0	0	—	65	
17	30	0	246	0	0	—	65	Fast day.
18	35	5	600	0	0	—	65	
19	35	5	600	0	0	—	64	
20	35	5	600	0	0	121	—	
21 to 24	35	5	600	0	0	—	66	
24	35	5	600	0	0	106	—	
25	40	5	700	0	0	—	66	
26	30	1	170	0	faint	—	65	Fast day.
27	40	5	700	0	faint	—	65	
28	40	5	700	0	0	106	—	
29 & 30	40	5	800	0	0	—	65	

TABLE IV. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
July								
1	40	5	800	0	0	115	—	
2 to 5	40	5	800	0	0	—	66	
5	40	5	800	0	0	124	66	
6 & 7	35	5	700	0	0	—	63	
8	35	5	700	0	faint	111	64	
9 to 15	40	5	800	0	0	—	64	
15	40	5	800	0	faint	99	64	
16 to 19	45	10	950	0	0	—	—	
19	45	10	950	0	0	214	—	
20 to 23	45	10	950	0	0	—	65	
23	45	10	950	0	faint	175	—	
24	30	1	200	0	0	—	64	Fast day.
25 to 30	40	5	800	0	0	—	64	
30	40	5	800	0	0	120	—	
31	25	2	200	0	0	—	64	Fast day.
August								
1 to 4	40	5	800	0	0	—	65	
4	40	5	1100	0	0	—	—	
5	40	5	1100	0	0	178	—	
6	40	5	1100	0	0	—	65	
7	30	1	187	0	0	—	64	Fast day.
8	45	5	1100	0	0	—	—	
9	45	5	1100	0	0	187	—	
10	45	5	1100	0	0	—	—	
11	45	5	1100	0	0	—	65	
12 to 15	45	5	1100	0	0	—	—	Patient at home on weighed diet.
15	30	5	—	0	0	—	—	Fast day.
16 to 23	45	5	1100	0	0	—	—	
23	30	5	—	0	0	—	—	Fast day.
24 to 31	45	5	1100	0	0	—	—	
31	30	5	—	0	0	—	—	Fast day.
September								
1 to 8	45	5	1100	0	0	—	—	
8	30	5	—	0	0	—	—	Fast day.
9	45	5	1100	0	0	—	—	Readmitted.
10 & 11	45	5	—	0	0	—	66	
12	30	10	—	0	0	200	67	
13 to 16	30	—	—	0	0	—	65	
16	30	5	500	0	0	120	65	
17 to 20	30	5	500	0	0	—	65	
20	30	5	500	0	0	127	—	
21 & 22	30	5	500	0	0	—	65	
23	35	5	700	0	0	—	65	
24	35	5	700	0	0	150	—	
25 & 26	30	5	700	0	0	—	65	
27	35	5	700	0	0	136	—	
28	35	5	700	0	0	—	66	
29 & 30	35	5	700	0	0	—	65	
October								
1	35	5	700	0	0	—	65	
2	—	10	—	0	0	—	65	Fast day.
3	35	5	700	0	0	171	—	
4 to 7	35	5	700	0	0	—	65	
7	35	5	700	0	faint	154	64	
8	35	5	700	0	0	—	—	
9	—	10	—	0	0	—	64	Fast day.
10	35	5	700	0	0	—	64	
11	35	5	700	0	0	146	63	

TABLE IV. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Oct.-Con.								
12 & 13	35	5	700	0	faint	—	62	
14	35	5	700	0	0	156	—	
15	35	5	700	0	0	—	64	
16	fast	day	—	0	0	—	—	
17 & 18	30	5	700	0	0	—	63	
19	30	5	700	0	0	136	62	
20	30	5	700	0	0	—	63	
21	30	5	700	0	0	146	64	
22	30	5	700	0	0	—	—	
23	2	10	—	0	0	—	—	Fast day.
24	25	5	133	0	0	—	63	
25	25	5	161	0	0	180	—	
26	25	5	161	0	0	200	64	
27	25	5	161	0	0	189	64	Lipemia
28	25	5	161	0	0	175	64	
29	25	5	161	0	0	—	64	
30	100	-fat	900	0	0	—	—	
31	25	—	137			—	—	
November								
1	25	—	161	0	0	—	68	
2 & 3	25	—	161	0	0	—	68	
4	25	—	161	0	0	142	68	
5	25	—	161	0	0	—	67	
6	—	10	—	0	0	—	67	Fast day.
7	25-1	68 fat	-1612	0	0	—	67	
8	50	10	1000	0	0	102	67	
9 & 10	50	10	1000	0	0	—	67	
11	50	10	1000	0	0	125	67	
12	50	10	1000	0	0	—	—	
13	30	5	311	0	0	—	69	Fast day.
14	50	10	1000	0	0	—	68	
15	50	10	1000	0	0	169	67	
16 & 17	50	10	1000	0	0	—	66	
18	50	10	1000	0	0	230	—	
19	50	10	1000	0	0	—	65	
20	10	—	40	0	0	—	65	Fast day.
21	15	—	99	0	0	—	65	
22	15	—	99	0	0	171	65	
1921								
November								
23	40	10	800	0	0	154	—	
24	50	10	1000	0	0	—	—	
25	40	10	800	0	0	—	65	
26	40	10	800	0	0	—	—	
27	15	10	160	0	0	—	64	Fast day.
28	40	10	800	0	0	153	64	
29 & 30	40	10	800	0	0	—	—	
December								
1	40	10	800	0	faint	182	—	
2 to 6	40	2	800	0	0	—	64	
6	40	2	800	0	0	206	—	
7 & 8	40	2	800	0	0	—	—	
9	40	2	800	0	0	195	65	
10 & 11	40	2	800	0	0	—	65	
12	10	2	—	0	0	—	—	Fast day.
13	40	2	800	0	0	166	—	
14	30	5	—	0	0	203	—	Fast day.
15	35	5	600	0	0	173	65	
16	35	5	600	0	0	—	—	

TABLE IV. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Dec.-Con.								
17	35	5	600	0	0	173	—	Fast day.
18	30	1	—	0	0	—	65	
19	35	5	600	0	0	—	—	
20	35	5	600	0	0	162	65	
21 & 22	35	5	600	0	0	—	64	
23	35	5	600	0	0	182	—	
24	30	0	600	0	0	—	64	
25	30	5	600	0	0	—	65	
26	30	0	600	0	0	173	—	
27 to 30	30	0	600	0	0	—	65	
30	30	0	600	0	0	173	—	
31	30	0	600	0	0	—	—	
1922								
January								
1 to 4	30	0	600	0	0	—	64	Fast day.
4	30	—	—	0	0	160	64	
5 to 8	30	0	600	0	0	—	64	
8	23	2	600	0	0	139	—	
9 & 10	30	0	600	0	0	—	65	
11	30	0	600	0	0	142	—	
12 to 17	30	0	600	0	0	—	65	
17	30	0	600	0	0	178	—	
18	30	0	600	0	0	—	64	
19 & 20	30	0	500	0	0	—	64	
21	30	0	500	0	0	152	—	
22	30	0	125	0	0	—	64	Fast day.
23	30	0	500	0	0	—	—	
24	30	0	300	0	0	—	64	
25	30	0	500	0	0	129	—	
26 to 29	30	0	500	0	0	—	64	Fast day.
29	30	0	125	0	0	—	63	
30	30	2	500	0	0	—	64	
31	30	2	500	0	0	136	—	
February								
1 to 7	30	2	500	0	0	—	—	Fast day.
7	30	2	500	0	0	106	64	
8 & 9	35	2	500	0	0	—	—	
10	35	2	500	0	0	103	—	
11	40	5	850	0	0	—	63	
12	40	5	600	0	0	—	—	
13	40	5	650	0	0	102	—	
14 & 15	45	5	800	0	faint	—	62	
16	45	5	800	0	0	162	—	
17 to 21	45	3	750	0	0	—	62	
21	45	3	750	0	0	118	—	
22 to 25	45	3	750	0	0	—	62	
25	45	3	750	0	0	150	—	
26	30	3	—	0	0	—	—	
27	45	3	800	0	0	—	62	
28	45	3	800	0	0	162	—	
March								
1 to 4	45	3	800	0	0	—	63	Fast day.
4	45	3	800	0	0	160	—	
5 to 11	45	3	800	0	0	—	63	
11	45	3	800	0	0	172	—	
12	20	—	—	0	0	—	—	
13	45	3	800	0	0	—	63	
14	45	3	800	0	0	140	—	
15 to 18	45	3	800	0	0	—	62	

TABLE V.

Case No. 23.

Date	DIET			Qualitative Dextrose in Urine	Qualitative Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
1919 August 1				mod.	mod.	441	66	Plasma nitroprusside moderate. Ditto.
5	fast	day		mod. slight	mod. slight	410	66	
6 to 13						—	69	Whiskey qs. ad. 360 calories.
13 to 15	30	1	360	slight	slight	—	—	
15	fast	day	—	trace	faint	205	69	
16 to 19	20	—	150	0	faint	—	67	
20	fast	day	—	0	faint	250	—	
21 to 23	22	—	600	faint	faint	—	67	
23	22	—	600	faint	faint	268	68	
24	fast	day	—	0	faint	—	—	
25	15	—	400	0	faint	188	—	
26 to 31	15	—	400	0	faint	—	69	
31	fast	day	—	0	faint	—	70	
September 1 to 3	15	—	400	0	faint	150	68	
4	—	—	—	0	faint	150	72	
4 to 8	15	—	—	0	faint	—	71	
8	—	—	—	0	faint	127	71	
8 to 13	20	—	400	0	faint	—	71	
13	20	—	500	0	0	—	69	
14	fast	day	—	0	faint	—	—	
15	25	—	600	0	faint	115	68	
16 to 20	25	—	600	0	faint	—	69	
20	fast	day	—	0	0	161	68	
22 to 30	30	—	700	0	faint	—	72	
October 1	fast	day	—	0	0	—	73	Specimen taken dur- ing digestion.
2	30	—	700	0	0	—	—	
3	21	—	665	0	faint	161	—	
4 to 9	30	—	700	0	faint	—	71	
9	30	—	700	0	faint	212	—	
10 to 11	30	—	700	0	faint	—	—	Plasma nitroprusside negative.
12	fast	day	—	0	faint	—	71	
13	30	—	700	0	faint	192	71	
14	30	—	700	0	faint	—	—	
15 to 17	30	—	500	0	faint	—	72	
18	30	—	500	0	faint	139	71	
19 to 25	30	5	500	0	faint	—	—	
26	fast	day	—	0	faint	155	70	
26 to 31	30	5	500	0	faint	—	—	
November 1	30	5	500	0	faint	—	71	
2	fast	day	—	0	faint	—	—	Cataracts needed. Vision improved.
3	30	5	500	0	faint	—	—	
4 to 9	30	10	600	0	faint	—	—	
9	fast	day	—	0	faint	—	—	
10	30	10	600	0	faint	120	68	

TABLE V. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Nov.-Con.								
11 to 16	30	10	600	0	faint	—	68	
16	fast	day	—	0	faint	—	67	
17 & 18	30	10	600	0	faint	—	—	
19	30	10	600	0	0	174	—	
20 to 23	30	5	600	0	0	—	67	
23	fast	day	—	0	faint	—	—	
24 to 27	30	5	600	0	0	—	69	
27	35	10	720	0	0	—	—	
28	30	5	600	0	faint	—	—	
29	30	5	600	0	0	139	—	Blood urea 20.
30	fast	day	—	0	faint	—	69	
December								
1 to 5	30	5	600	0	0	—	70	
5	30	5	600	0	0	128	—	
6	30	5	600	0	faint	—	—	
7	fast	day	—	0	faint	—	68	
8 to 12	30	5	600	0	0	—	—	
12	30	5	600	0	0	142	—	
13	30	5	600	0	0	—	—	
14	fast	day	—	0	faint	—	68	
15 to 19	40	0	600	0	0	—	—	
19	40	0	600	0	faint	135	—	
20	40	0	600	0	0	—	—	
21	fast	day	—	0	0	—	68	
22 to 25	40	0	600	0	faint	—	—	
25	50	6	700	0	0	—	—	
26 & 27	40	0	600	0	0	—	68	
28	fast	day	—	0	0	—	—	
29	40	0	600	0	faint	—	—	
30	40	0	600	0	0	169	68	
31	40	0	600	0	0	—	—	
1920								
January								
1	40	0	600	0	0	—	—	
2	39	0	693	0	0	—	—	
3	50	0	671	0	0	—	—	
4	25	0	127	0	0	—	—	Fast day.
5	50	0	650	slight	faint	226	66	
6	28	7	297	faint	faint	—	—	
7	40	0	670	0	0	—	—	
8	40	0	670	0	0	—	—	
9	40	0	670	0	faint	—	—	
10	40	0	670	faint	0	—	66	
11	15	0	109	0	0	—	—	Fast day.
12	53	0	600	0	0	187	—	
13	48	0	783	0	0	—	—	
14	38	0	719	0	0	—	—	
15	48	0	732	0	0	—	—	
16	47	0	728	0	0	—	—	
17	51	0	681	0	0	192	—	
18	51	0	681	heavy	0	—	65	
19	fast	day	—	0	0	—	—	
20	50	0	650	0	0	—	—	
21	fast	day	—	heavy	0	342	—	
22 to 25	53	0	689	0	0	—	—	
25	10	0	50	0	0	—	—	Fast day.
26	40	0	594	0	0	—	—	
27	40	0	594	0	0	285	—	
28	15	—	—	faint	0	290	65	Fast day.

TABLE V. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Jan.-Con.								
29 to 31	40	0	600	0	0	—	—	
31	40	0	600	0	0	—	—	
February								
1	10	15	—	faint	0	—	—	
2	40	0	592	heavy	0	—	—	
3	16	9	187	slight	0	—	—	
4	fast	day	—	0	0	220	—	
5	fast	day	—	0	0	—	—	
6	30	0	500	0	0	157	66	
7	30	0	500	0	0	—	—	
8	10	—	—	0	0	—	—	Fast day.
9	30	0	500	0	0	—	—	
10	30	0	700	slight	0	384	—	
11	30	0	696	slight	faint	—	—	
12	15	—	—	faint	0	—	—	
13	fast	day	—	0	0	—	—	
14	50	0	500	0	0	182	67	
15	50	5	800	0	0	178	—	
16	50	5	800	heavy	0	300	—	
17	50	5	800	heavy	0	428	—	
18	25	3	400	faint	0	405	—	
19	25	3	400	heavy	0	319	—	
20	25	3	400	heavy	0	416	—	
21	8	—	—	faint	0	—	—	
22	fast	day	—	heavy	0	—	66	
23	15	0	159	faint	0	—	—	
24	15	0	159	faint	0	340	—	
25	fast	day	—	faint	0	—	—	
26	23	0	261	0	0	—	—	
27	23	0	250	0	0	306	—	
28	22	0	108	0	0	255	65	
29	22	0	234	0	0	290	—	
March								
1	15	0	159	0	0	217	—	
2	23	0	256	0	0	220	—	
3	23	0	256	0	0	192	66	
4	23	0	256	0	0	214	—	
5	23	0	256	0	0	209	—	
6	23	0	256	0	0	189	—	
7	23	0	256	0	0	159	—	
8	fast	day	—	0	0	089	—	
9	50	0	540	0	0	—	—	
10 to 13	50	0	400	0	0	—	—	
13	50	3	700	0	0	092	67	
14	50	3	700	0	0	—	—	
15	50	3	700	0	0	136	—	
16	50	3	700	0	0	175	—	
17	40	0	700	0	0	—	—	
18	40	0	500	0	0	254	—	
19	40	0	500	0	0	—	—	
20	40	0	500	0	0	—	—	
21	20	0	300	0	0	127	66	
22	40	0	500	0	0	075	—	
23 & 24	40	0	500	0	0	—	—	
25	40	0	500	0	0	140	—	
26	40	0	500	0	0	—	—	
27	40	0	500	0	0	133	—	
28	20	—	—	0	0	—	—	Fast day.
29	40	0	500	0	0	192	65	

TABLE V. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Mar.-Con.								
30	40	0	500	0	0	122	—	
31	40	0	500	0	0	—	—	
April								
1 & 2	40	0	500	0	0	—	—	
3	40	0	500	0	0	089	65	Discharged from Institute. Patient went home on accu- rately weighed diet.
11	40	0	500	0	0	105	—	Patient at home. Takes weekly fast day of 20 gm. protein.
12	45	5	500	0	0	—	—	Patient at home. Takes weekly fast day of 20 gm. protein.
18	45	5	500	0	0	111	65	Patient at home. Takes weekly fast day of 20 gm. protein.
19	50	10	500	0	0	—	—	Patient at home. Takes weekly fast day of 20 gm. protein.
May								
2	50	10	500	0	0	080	—	Patient at home. Takes weekly fast day of 20 gm. protein.
3	50	10	500	0	0	086	—	Patient at home. Takes weekly fast day of 20 gm. protein.
16	50	10	500	0	0	089	—	Patient at home. Takes weekly fast day of 20 gm. protein.
19	50	5	600	0	0	103	—	Patient at home. Takes weekly fast day of 20 gm. protein.
29	50	5	600	0	0	081	64	Patient at home. Takes weekly fast day of 20 gm. protein.
30	50	3	700	0	0	—	—	Patient at home. Takes weekly fast day of 20 gm. protein.
June								
4	50	3	700	0	0	119	—	Patient at home. Takes weekly fast day of 20 gm. protein.
25	50	3	700	0	0	118	65	Patient at home. Takes weekly fast day of 20 gm. protein.

TABLE V. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
July								
1	50	3	700	faint	0	—	—	Faint traces of sugar in urine.
6	50	3	700	0	0	—	—	Re-admitted to Insti- tute.
7	50	3	700	0	0	155	65	
8	50	3	700	0	0	213	—	
9	50	3	700	0	0	201	—	
10 to 17	50	3	700	0	0	—	65	
17	20	—	—	0	0	—	—	Fast day.
18 to 25	50	3	700	0	0	—	64	
25	20	—	—	0	0	—	—	Fast day.
26 to 29	50	3	700	0	0	—	64	
29	50	3	700	faint	0	—	—	
30	20	—	—	0	0	—	—	Fast day.
31	20	—	—	0	0	179	63	Fast day.
August								
1	30	1	400	0	0	—	—	
2	40	1	500	0	0	100	—	
3	40	1	500	0	0	072	—	
4	50	1	600	0	0	—	—	
5	50	1	600	0	0	—	63	
6	20	—	—	0	0	089	—	Fast day. Patient discharged.
7 to 31	40	1	650	0	0	—	—	At home on weighed diet. No glyco- suria. Weekly fast days of 20 gm. protein.
September								
1 to 20	40	1	650	0	0	—	61	Weekly fast days of 20 gm. protein.
21	40	1	650	0	0	272	—	Faint glycosuria.
22	20	—	—	0	0	—	—	Re-admitted to Insti- tute.
23	20	0	134	0	0	—	—	
24	20	0	152	0	0	129	61	
25	40	0	400	0	0	103	—	
26 & 27	40	0	600	0	0	—	—	
28	40	0	600	0	0	100	—	
29	50	0	700	0	0	127	61	
30	50	0	700	0	0	—	—	
October								
1	15	—	—	0	0	—	—	Fast day.
2	50	0	700	0	0	—	61	
3	50	0	600	0	0	145	—	Discharged from Institute.
4 to 31	50	0	600	0	0	—	62	On weighed diet. Weekly fast days of 20 gm. protein.
November								
1	50	2	600	0	0	—	—	Re-admitted to Insti- tute.
2 to 5	50	2	600	0	0	—	—	
5	20	0	125	0	0	296	—	
6	40	2	400	0	0	—	60	
7 & 8	50	2	500	0	0	—	—	
9	50	3	600	0	0	093	—	
10	50	3	600	0	0	—	—	
11	40	0	340	0	0	201	—	

TABLE V. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Nov.-Con.								
12	40	0	400	0	0	093	—	
13	50	2	500	0	0	168	60	
14	50	2	500	0	0	—	—	
15	50	2	500	0	0	168	—	
16	50	2	500	0	0	195	—	
17 & 18	50	2	500	0	0	—	—	
19	20	—	—	0	0	—	—	Fast day.
20	50	2	500	0	0	116	—	
21	50	2	500	0	0	080	—	
22 & 23	50	2	500	0	0	—	—	
24	50	2	500	0	0	152	60	
25	50	2	500	0	0	—	—	
26	25	0	165	0	0	—	—	Fast day.
27	50	2	500	0	0	045	—	
28	50	2	500	0	0	—	—	
29	50	2	500	0	0	204	—	
30	50	2	500	0	0	—	—	
December								
1	40	2	500	0	0	—	—	
2	40	2	500	0	0	—	—	
3	25	0	179	0	0	157	59	
4	40	2	500	0	0	—	—	
5	40	2	500	0	0	094	—	
6	50	3	500	0	0	—	—	
7	50	3	500	0	0	245	—	
8	50	3	500	0	0	—	59	
9	50	3	500	0	0	112	—	Discharged. Weekly fast day of 20 grams protein.
1921								
January	45	2	500	0	0	—	58	Free from hypergly- cemia. Weekly fast days of 20 grams protein.
February	45	2	650	0	0	—	59	Free from hypergly- cemia. Weekly fast days of 20 grams protein.
March	40	5	700	0	0	—	57	Free from hypergly- cemia. Weekly fast days of 20 grams protein.
April								
1	40	3	800	0	0	082	—	Re-admitted to Insti- tute.
2	40	3	800	0	0	—	59	
3	30	—	—	0	0	—	—	Fast day.
4	40	3	800	0	0	083	60	
5 to 9	40	3	800	0	0	—	59	
9	40	3	800	0	0	142	—	
10	25	0	208	0	0	—	—	Fast day.
11 to 16	40	3	650	0	0	—	—	
16	40	3	650	0	0	098	59	
17	25	1	—	0	0	—	—	Fast day.
18	40	3	650	0	0	—	—	
19	40	3	650	0	0	075	—	Cataracts needed. Vision improved.
20 & 21	40	3	650	0	0	—	—	

TABLE V. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
Apr -Con.								
22	40	3	650	0	0	108	59	
23	40	3	650	0	0	—	—	
24	25	1	—	0	0	—	—	Fast day.
25 to 30	40	5	700	0	0	—	—	
30	40	5	700	0	0	164	59	Faint lipemia.
May								
1	15	10	140	0	0	—	—	Fast day.
2	25	2	400	0	0	138	—	
3 & 4	40	5	500	0	0	—	—	
5	40	5	500	0	0	142	56	
6	40	5	500	0	0	143	—	
7	40	5	500	0	0	—	—	
8	25	0	194	0	0	—	—	Fast day.
9	40	5	500	0	0	—	—	
10	40	5	500	0	0	100	—	
11 & 12	40	5	500	0	0	—	—	
13	40	5	500	0	0	077	57	
14	40	5	600	0	0	—	—	
15	30	2	227	0	0	—	—	Fast day.
16 to 21	40	5	600	0	0	—	—	
21	40	5	600	0	0	150	—	
22	20	1	138	0	0	—	56	Fast day.
23	40	5	600	0	0	—	—	
24	40	5	600	0	0	094	—	
25 to 28	40	5	600	0	0	—	—	
28	40	5	600	0	0	076	—	
29	25	1	173	0	0	—	—	Fast day.
30	40	5	700	0	0	—	55	
31	40	5	700	0	0	093	—	
June								
1	40	5	700	0	0	—	54	
2	40	5	700	0	0	094	—	
3 & 4	55	10	700	faint	0	—	—	
5	26	6	464	0	0	136	—	
6	55	10	700	faint	0	—	53	
7	55	10	700	faint	0	173	—	
8 & 9	45	10	700	faint	0	—	—	
10	45	10	700	heavy	0	220	48	
11	45	10	700	mod.	0	—	—	
12	40	5	600	0	0	075	—	
13	40	5	600	0	0	—	—	
14	40	5	600	0	0	112	50	
15	40	5	600	v. faint	0	—	—	
16	20	2	324	0	0	238	—	
17	15	0	80	0	0	173	54	Fast day.
18	30	5	400	0	0	107	—	
19	40	5	500	0	0	113	59	
20 to 25	40	5	500	0	0	—	—	
25	40	5	500	0	0	169	62	
26	25	3	—	0	0	—	—	Fast day.
27	35	5	450	0	0	—	—	
28	35	5	450	0	0	108	66	
29 & 30	35	5	550	0	0	—	—	
July								
1	35	5	550	0	0	175	64	
2 to 5	35	5	450	0	0	—	—	
5	35	5	450	0	0	162	—	
6 to 9	30	5	450	0	0	—	—	
9	30	5	450	0	0	097	64	

TABLE V. (Continued)

Date	DIET			Qualita- tive Dextrose in Urine	Qualita- tive Nitro- prusside in Urine	Plasma Sugar Mg. per 100 c.c.	Body Weight Pounds	Remarks
	Protein Grams	Carbo- hydrate Grams	Total Calo- ries					
July.—Con.								
10	35	5	500	0	0	—	—	
11	35	5	500	0	0	133	—	
12	35	5	500	0	0	—	—	
13	30	5	500	0	0	—	—	
14 to 16	30	5	500	0	0	—	66	
16	30	5	500	0	0	127	—	
17	30	—	—	0	0	—	—	Fast day.
18	30	5	500	0	0	—	—	
19	30	5	500	0	0	106	—	
20	35	5	550	0	0	—	—	
21	35	5	550	0	0	—	65	
22	35	5	550	0	0	136	—	
23	35	5	550	0	0	—	—	
24	25	—	—	0	0	—	—	Fast day.
25	35	5	550	0	0	—	—	
26	35	5	550	0	0	166	—	
27	35	5	550	0	0	—	—	
28	30	5	500	0	0	—	64	
29	30	5	500	0	0	142	—	
30	30	5	500	0	0	—	—	
31	33	3	—	faint	0	—	—	Fast day.
August								
1	30	5	500	faint	0	—	63	
2	30	5	500	faint	0	—	58	
3 & 4	15	3	300	0	0	—	—	
5	15	3	400	0	0	260	57	
6	15	3	400	0	0	—	57	
7	15	3	400	0	0	106	57	
8	15	0	350	0	0	—	—	
9	15	0	350	0	0	128	—	
10 & 11	15	0	350	0	0	—	—	
12	15	0	350	0	0	082	56	
13	15	0	350	0	0	—	—	Patient died.

METABOLISM STUDIES IN TETANY

By FRANK P. UNDERHILL, WILDER TILESTON AND JEAN BOGERT

*From the Department of Pharmacology, and the Ssection of
Internal Medicine, Yale University, School of Medicine,
New Haven.*

The purpose of this communication is to present the results of an investigation in a case of tetany of intestinal origin. No attempt will be made to renew the literature upon the topic, since the viewpoints relative to tetany in general are so at variance as to put the whole subject in a chaotic state. Before clearly defined opinions can be formulated, much careful and extensive observation must be made. To this end the following data are contributed.

PLAN OF INVESTIGATION.

The general plan of investigation was so outlined as to include as many different types of determinations as was practicable. In accord with this the metabolism has been studied with respect to nitrogen, fat and calcium. In general, since calcium has become associated with tetany the experiments were planned so as to give emphasis to calcium exchange. The dietary was limited in the kind of food, and was so selected as to be poor in calcium. It was restricted within certain limits but was not a constant diet. Calcium was added to this in the form of milk. The investigation covered three 5-day periods. Period 1 was arranged so as to present a calcium-low diet. Period 2 represented a calcium-rich diet. This was accomplished by the addition of varying quantities of milk. Period 3 was approximately identical with Period 1; that is, a period low in calcium, milk being withdrawn from the dietary.

The experimental periods were marked off in the feces by the employment of carmine. Calcium was determined in the food, urine, and feces by the methods of McCruden¹. Nitrogen in the food, urine and feces was estimated by the Kjeldahl method, hydrogen ion concentration in urine by the method of

Henderson and Palmer²; total acidity, ammonia, creatinine and creatinine and phenols by Folin's methods; organic acids by essentially the method of Van Slyke and Palmer³; phosphates by precipitation with uranium, and sulphur by Benedict's method; indican was estimated by Ellinger's permanganate method.

Fat in food and feces signifies ether extract, the extraction being accomplished by the Soxhlet apparatus upon the air dried materials.

Calcium in the blood was determined according to Marriott and Howland⁴.

The dietary followed closely that outlined in a previous study in calcium and magnesium metabolism⁵ and the details will therefore be omitted here. Two normal subjects taken as standard in the above cited communication have been employed again in the present report.

DESCRIPTION OF SUBJECTS.

Subject 1. — M. A., female, age 25 years; engaged in laboratory work. The experiment was so planned that menstrual periods were avoided.

Subject 2. — G. S., male, age 28 years; engaged in laboratory work.

Subject 3. — A. B., an Italian housewife.

A. B., an Italian woman, 35 years of age, was first admitted to the New Haven Hospital April 25, 1919 (No. 71311) discharged May 18, 1919, re-admitted June 3, 1919 (No. 71724) and discharged July 17, 1919.

Present illness. She had influenza in October 1918, was in bed eight weeks and lost much weight and strength. After this illness she suffered from diarrhea, alternating with short periods of constipation, and associated with vague abdominal pains. Four weeks previous to admission she began to suffer from attacks of cramps in the hands, feet and neck.

The past history and the family history were unimportant.

Physical examination at the hospital showed as the important points the following: marked emaciation, a fine tremor of the upper lip and eyelids, positive Trousseau's and Chvostek's signs, and attacks of spasm of the hands and feet in which the characteristic position of tetany was noted. The electrical reactions, taken on several occasions, were typical of tetany; e.g., on May 2nd the following figures were obtained: K.C.C. 0.4 milliampere, A.C.C. 1.8, A.O.C. 0.8, K.C. tetanus 0.7.

The *urine* showed the slightest possible trace of albumin, no sugar, and a marked excess of indican. (For other data see tables further on.)

The *stools* were liquid throughout her stay in the hospital, and contained much fat in the form of neutral fat and fat needles. Examinations for trypsin by the Gross method showed 50 units and 250 units on two occasions.

The CO₂ combining power of the blood on April 30th was 90 volumes per cent by the Van Slyke method.

Diagnosis. The diagnosis of tetany was very evident. The nature of the diarrheal affection remained obscure, in spite of careful examinations by the Roentgen-ray, test meals, etc.

Medication. No drugs were given during the period of metabolic study, except on June 14th and 15th, when five doses of tincture of opium, 10 minims each, were given to control the diarrhea.

The administration of calcium appeared to control the tetany, and pancreatin had a favorable, though temporary, effect on the fatty diarrhea.

Progress of the disease. The diarrhea continued and emaciation became extreme, the weight falling from 71 pounds on April 25th to 55 pounds on July 16th.

The patient died at home in August 1919. An autopsy was not permitted.

CALCIUM METABOLISM IN TETANY.

CALCIUM BALANCE.

In Table I are presented data relative to the calcium balance in the different periods. In the first period the subject is in slight negative balance, which might be expected upon such a restricted calcium intake. During the period (Period 2) of high calcium intake this element was stored to a large extent, a calcium balance of nearly three grams being obtained. In the following low calcium period a negative balance again obtained, indicating that the retention of calcium in the previous period was only temporary; when the subject was placed in a condition of low calcium intake the stored calcium was excreted.

With respect to the calcium balance the tetany subject behaves in a manner entirely analogous to normal individuals, except that relatively more calcium is retained.

FURTHER ANALYSIS OF THE DATA

Excretion of Added Calcium. — If one tests the ability of the organism in tetany to excrete added calcium, the figures in Table II will attest to the correctness of the statement that calcium added to the diet is at least temporarily retained, judging by comparative data obtained with normal individuals.

Relation of Calcium Output to Intake. — The data in Table III indicate that on a low calcium diet the relation of output to intake is distinctly normal. When, however, calcium

TABLE I.
Calcium Balance in Tetany.

Period	Diet	Date 1919 June	CALCIUM			
			Intake mg.	Output		Balance mg.
				Urine mg.	Feces mg.	
1	Calcium Low	4	215	24	—	—
		5	346	23	—	—
		6	117	23	—	—
		7	108	17	—	—
		8	108	21	—	—
Total			894 — 50 = 844	108	911	— 175
				1019		— 35
Average per day			169	21	182	
				203		
2	Calcium High	9	1678	17	—	—
		10	1665	23	—	—
		11	1195	30	—	—
		12	1392	17	—	—
		13	1231	29	—	—
Total			7161	116	4147	+2898
				4263		
Average per day			1432	23	829	+ 579
				852		
3	Calcium Low	14	202	29	—	—
		15	104	21	—	—
		16	129	26	—	—
		17	192	21	—	—
		18	186	21	—	—
Total			823 — 41 = 772	118	2085	—1431
				2203		
Average per day			154	23	417	— 286
				440		

is added in large measure, the subject with tetany evinces a greater tendency to store calcium than does the normal individual, and when the calcium-poor ration is resumed, calcium is lost to a much greater degree with the tetany patient than with the normal subjects. From this it might appear perhaps that calcium regulation in the tetany subject is much less stable than normally.

The Relation of Calcium Output to Intake for the Entire Period. — Comparing the calcium output to the intake for the entire period for the tetany case, with similar data for normal subjects, one derives the conclusion that in the case of tetany there is a much greater tendency for calcium storage than with the normal cases. This is well brought out if one averages the intake and output in the normal cases and compares these

TABLE II.

Excretion of Added Calcium

S U B J E C T		Excretion of Added Calcium Per cent.
Subject 1 — Normal	100+
“ 2 — “	92+
“ 3 — Tetany	68+

TABLE III.

Relation of Calcium Output to Intake.

$$\text{Ratio} = \frac{\text{Calcium Output}}{\text{Calcium Intake}}$$

S U B J E C T		P E R I O D		
		1	2	3
Subject 1 — Normal	1.6	1.0	1.9
“ 2 — “	1.2	0.9	1.7
“ 3 — Tetany	1.2	0.5	2.9

figures with similar data for the tetany case. The comparison is not exact, inasmuch as the data for the normal subjects is taken for periods of 13 days and 14 days, whereas that of the tetany subjects is for a period of 15 days. Nevertheless the comparison brings out the desired point clearly, since even with the possible disadvantage of a longer time interval, the tetany subject demonstrates a marked ability to retain cal-

cium. Even though a strict comparison is made by various methods of calculation the essential fact remains unchanged. The distinct tendency to retain calcium might be interpreted to indicate a need for this element on the part of the tetany individual.

The Relation of Calcium Intake and Output to Body Weight. — Differences in body weight will not explain the different manner in which calcium is handled by the tetany subject, since the same type of peculiarity is brought out in normal subjects where the relation of calcium intake and output is compared to body weight referred to analogous data.

Absorption of Calcium. — In a previous communication⁵ it is stated — “a point of considerable interest in the interpretation of the data presented, relates to the question of variation in absorption of the introduced calcium. It is obvious that this question does not lend itself readily to dogmatic statements, since it is probable that calcium is excreted in variable degree by both the kidney and intestines, under diverse circumstances. In this consideration the excretion of calcium through the urine is taken tentatively as evidence of absorption; the passage of calcium through the feces as unabsorbed calcium. This is obviously incorrect, since undoubtedly part of the calcium eliminated with the feces is calcium which underwent absorption, and is merely excreted by the intestine. For a comparative study of absorption, however, such a hypothesis may be employed”.

“On the basis of this hypothesis, with the necessary limitations involved, a study of the excretion of calcium by way of the urine in relation to the intake shows some noteworthy features. With normal individuals on a calcium-low diet, approximately one-half, to a quantity equal to the ingested calcium, is excreted by way of the kidney. As a calcium-rich diet is introduced, the relative quantity of food calcium absorbed diminishes to a perceptible degree. Withdrawal of the calcium-rich diet causes the relation between the calcium excreted by the kidney and that ingested, to resume the status which was obtained in the calcium-poor period previously”.

With the case of tetany (see Table VI) the ratio is radically different from that of the normal individuals. Very little calcium is eliminated by way of the urine either on a calcium-poor or a calcium-rich diet and changing the calcium intake

TABLE IV.

Relation of Calcium Output to Intake for the Entire Period.

SUBJECT	Output mg.	Difference mg.	Intake mg.
Subject 1—Normal	10,443 (13 days)	7,583	—2,860
“ 2— “	12,626 (14 “)	9,752	—2,874
“ 3—Tetany	7,485 (15 “)	8,777	+1,292

TABLE V.

Relation of Calcium Intake and Output to Body Weight.

SUBJECT	Body Weight lbs.	CALCIUM		Calcium per pound of Body Weight	
		Intake mg.	Output mg.	Intake mg.	Output mg.
Subject 1—Normal	105	7,583	10,443	72	99
“ 2— “	150 (13 days)	9,752	12,626	65	84
“ 3—Tetany	62	8,777	7,485	141	120

affects very little if at all the amount of calcium excreted by kidney.

Relation of Fecal Calcium to Calcium Intake.— Before one can draw positive conclusions relative to calcium absorption in tetany, the excretion of calcium by way of the intestine must be considered. From Table VII it is quite evident that a normal ratio obtains in Periods 1 and 2 thus indicating that in tetany calcium absorption proceeds in normal manner. This is corroborated by the data in Period 3 wherein it is shown that here for the first time the ratio diverges from the normal — indicating a great excretion by the intestine. This calcium, however, must be regarded as having undergone absorption for otherwise its delayed appearance in the stools is impossible of explanation, especially in view of the irritable state of the intestinal canal.

It is therefore, probable that in tetany calcium absorption proceeds within normal limits.

TABLE VI.

Relation of Urinary Calcium Excretion to Calcium Intake.

$$\text{Ratio} = \frac{\text{Calcium of Urine}}{\text{Calcium of Food}}$$

S U B J E C T		P E R I O D		
		1	2	3
Subject	1 — Normal	1.0	0.4	1.0
"	2 — "	0.4	0.2	0.5
"	3 — Tetany	0.1	0.01	0.1

TABLE VII.

Relation of Fecal Calcium to Calcium Intake.

$$\text{Ratio} = \frac{\text{Calcium of Feces}}{\text{Calcium of Food}}$$

S U B J E C T		P E R I O D		
		1	2	3
Subject	1 — Normal	0.6	0.6	0.8
"	2 — "	0.8	0.7	1.1
"	3 — Tetany	1.0	0.5	2.7

Relation of Urinary Calcium to Fecal Calcium. — Comparison of the output of calcium in the urine and feces (see Table VIII) shows that in tetany only a small proportion of absorbed calcium finds its exit from the body by way of the kidney. This ratio confirms previous statements.

CALCIUM IN THE BLOOD.

A few determinations have been made of the quantity of calcium in the blood of our tetany subject. The figures follow:

D A T E		C A L C I U M per 100 cc. serum m g m .	D I E T
1919			
May	10	6.0	Unrestricted
"	14	5.4	"
June	4	1.2 (?)	Low calcium (Period 1)
"	12	4.2	High " (" 2)

It is quite apparent that throughout the interval represented by the data, calcium in the blood was considerably lower than that of normal individuals. Apparently high calcium in-

take had little influence in appreciably increasing the calcium of the blood.

NITROGEN METABOLISM IN TETANY

Nitrogen Balance.—In view of the severe intestinal disturbance in this patient it was of interest to determine the nitrogen balance and nitrogen utilization during the periods of experimentation. The data incident to these determinations may be found in Table IX. These figures show that in spite of the intestinal disturbance the accompanying diarrhea and progressive loss of weight the patient was in positive nitrogen balance and that nitrogen utilization was excellent. Especially noteworthy in this connection is the unusually low fecal output of nitrogen.

It is quite evidente therefore that despite the serious condition of the patient, nitrogen metabolism as indicated by nitrogen balance and nitrogen utilization, was similar to that of normal individuals.

TABLE VIII.

Relation of Urinary and Fecal Calcium.

$$\text{Ratio} = \frac{\text{Calcium of Urine}}{\text{Calcium of Feces}}$$

SUBJECT		PERIOD		
		1	2	3
Subject 1	— Normal	1.5	0.6	1.1
" 2	— "	0.5	0.2	0.4
" 3	— Tetany	0.1	0.02	0.05

URINE ANALYSIS.

Analysis of the urine (Table X) shows as the most noteworthy feature an unusually high excretion of ammonia which is fairly constant on the average throughout the different periods. The cause for this augmented ammonia eliminated is difficult of explanation since urinalysis shows no other indication of acidosis, judged by the figures for pH, total acidity, and organic acids. Neither is there a relationship between the phosphorus and sulphur output, since these last two substances vary considerably in the different periods, whereas the ammonia excretion is fairly constant. Moreover it can hardly be

TABLE IX.
Nitrogen Balance in Tetany.

Period	Date	NITROGEN			
		Intake	Output		Balance
			Urine	Feces	
	1919 June	gm.	gm.	gm.	gm.
1 Low Calcium	4	5.16	5.26	—	—
	5	6.21	3.53	—	—
	6	2.97	3.48	—	—
	7	2.91	3.21	—	—
	8	3.88	3.88	0.40	—
Total		21.13	19.36	0.40	+ 1.37
			19.76		
Average per day		4.22	3.87	0.08	+ 0.27
			3.95		
2 High Calcium	9	6.26	3.91	—	—
	10	6.55	4.92	—	—
	11	7.49	4.90	—	—
	12	9.99	5.24	—	—
	13	9.22	4.98	0.31	—
Total		39.51	23.95	0.31	+15.26
			24.26		
Average per day		7.90	4.79	0.06	+ 3.05
			4.85		
3 Low Calcium	14	6.62	4.49	—	—
	15	3.26	4.45	—	—
	16	4.42	4.43	—	—
	17	6.11	4.60	—	—
	18	5.80	4.80	0.26	—
Total		26.21	22.77	0.26	+ 3.18
			23.03		
Average per day		5.24	4.55	0.05	+ 0.63
			4.60		

UTILIZATION OF NITROGEN

Period	Nitrogen Intake gm.	Nitrogen in Feces gm.	Utilization Per cent.
1	21.13	0.40	97
2	39.51	0.31	99
3	26.21	0.26	99

explained on the hypothesis of low nitrogen intake, since not only is the ammonia output high in relation to total nitrogen but the absolute quantity is above the usual excretion seen in normal individuals. From these considerations it is quite probable that ammonia excretion cannot be regarded as an evidence of acidosis. Some evidence has been reported ascribing to intestinal putrefaction the rôle of forming ammonia. Since excessive intestinal putrefaction was present in this instance, as indicated by increased phenols and indican⁶, it is quite probable that the excess of ammonia in the urine may be explained in this way.

Since Paton and his co-workers⁷ have ascribed to guanidine a leading rôle in the production of tetany an attempt was made to isolate this substance from the urine of this tetany subject. Employing the method of Koch as modified by Paton and his collaborators, a beautifully crystalline gold salt was isolated which on analysis by Dr. P. A. Levene proved to be an ammonia gold salt. Evidence of the presence of guanidine was therefore lacking.

METABOLISM OF FAT IN TETANY.

One essential feature relative to fat metabolism is the determination of fat utilization. From the figures in Table XI it is quite apparent that in this patient fat utilization was very poor throughout the period of observation. This poor fat utilization is undoubtedly closely associated with the severe intestinal disturbance and the marked loss of weight, and may perhaps account for the fact that very little calcium is excreted by way of the kidneys.

TABLE X.
Composition of the Urine in Tetany.

	Volume	Sp. Gr.	pH	Total Acidity	Total N	NH ₃ -N	Organic Acids	Creatine	Creatinine	Phenols			Indican	P	S
	c.c.	1.0-		c.c. N/10	gm.	mg.	c.c.	gm.	gm.	Total	Free	Conjugated	mg.	mg.	mg.
Diet Period 1 June	1470	11	6.8	177	5.26	1128	122	0.22	0.43	478	279	199	27	204	224
	1360	8	6.8	156	3.53	850	131	0.22	0.25	370	236	134	20	91	105
	1176	11	6.9	132	3.48	745	103	0.13	0.37	335	213	122	6	109	173
	1176	15	6.8	116	3.21	695	84	0.17	0.23	307	184	123	9	121	126
	1095	8	6.8	127	3.88	730	76	0.16	0.33	286	178	108	16	186	179
Average	1255	11	6.8	142	3.87	830 (21.5%)	103	0.17	0.32	355	218	137	16	142	161
Diet Period 2	1358	6	6.2	146	3.91	880	78	0.16	0.34	336	230	106	10	251	192
	1358	13	6.2	171	4.92	1009	88	0.19	0.36	269	269	242	27	307	221
	1398	9	6.2	149	4.90	974	78	0.24	0.34	407	260	147	20	262	242
	1433	7	6.6	157	5.23	1011	80	0.16	0.37	426	249	177	5	284	294
	1623	6	6.4	140	4.98	1082	78	0.11	0.35	461	289	172	0	228	274
Average	1434	8	6.3	152	4.79	991 (20.7%)	80	0.17	0.35	379	260	125	9	266	245
Diet Period 3	1665	8	7.0	144	4.49	1064	76	0.11	0.33	420	274	146	19	248	281
	1895	4	7.0	166	4.45	1041	95	0.09	0.39	361	263	98	2	263	259
	1325	5	6.8	106	4.43	953	41	0.10	0.34	349	227	122	2	238	256
	1940	6	6.8	143	4.60	1147	91	0.10	0.31	411	315	96	6	189	296
	1875	6	6.6	144	4.80	1106	73	0.20	0.35	446	294	152	0	260	274
Average	1740	6	6.8	141	4.55	1062 (23.3%)	75	0.12	0.34	397	274	127	5	240	273

TABLE XI.
Fat Balance in Tetany.

Period	Date 1919 June	F A T (=ether extract)			
		Intake Food gm.	Output Feces gm.	Balance gm.	Utilization Per cent.
1 Low Calcium	4	32.39	—	—	—
	5	56.30	—	—	—
	6	26.54	—	—	—
	7	38.28	—	—	—
	8	28.94	37.68	—	—
Total		182.45 — 8.96 vom- itus (on June 8) = 173.49	37.58	135.81	78
2 Calcium- Rich	9	33.75	—	—	—
	10	34.98	—	—	—
	11	34.73	—	—	—
	12	45.53	—	—	—
	13	42.01	80.00	—	—
Total		191.00	80.00	111.00	58
3 Low Calcium	14	42.03	—	—	—
	15	20.67	—	—	—
	16	24.06	—	—	—
	17	35.43	—	—	—
	18	31.99	—	—	—
Total		154.18 — 2.42 vom- itus (June 18) = 151.76	61.88	89.88	59

SUMMARY.

The subject with tetany when compared to normal individuals under the same experimental conditions shows a normal type of behavior to calcium intake, except that there is evidence of a greater tendency to store calcium temporarily,

on a calcium-rich diet. On the other hand, on a calcium-poor diet this stored calcium is eliminated to a much greater extent than occurs in the normal subject. These facts may be interpreted to mean that the organism with tetany shows a greater need for calcium than the normal individual, but that in tetany the regulation of calcium equilibrium is in an unstable condition.

In tetany, relatively little calcium is eliminated by way of the urine whether the subject ingests little or much calcium. Calcium absorption proceeds within normal limits in a condition of tetany. Even though relatively large amounts of calcium appear in the stools this represents in large measure excretion of absorbed calcium rather than the direct passage through the alimentary canal of ingested calcium.

If a tendency to retain calcium may be accepted as a criterion for calcium need, the data of this investigation suggest the desirability of calcium administration in tetany.

Calcium in the blood, in the patient under discussion, was significantly lower than that found in normal individuals. This was true whether the individual was maintained upon an unrestricted diet or upon a diet low or rich in calcium.

In tetany the patient may steadily lose weight and yet maintain a positive nitrogen balance, and exhibit a normal nitrogen utilization.

The most characteristic feature of the urinary excretion is the large output of ammonia, the elimination of which does not appear to be directly associated with other urinary evidences of acidosis.

Fat utilization in the tetany subject under discussion was very poor. It is probable that this result is associated with the accompanying severe diarrhea and the marked loss of body weight.

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STUDIES ON VITAMINES B AND D

BY CASIMIR FUNK AND JULIA B. PATON

*From the Biochemical Laboratory of Columbia University, at the College of Physicians and Surgeons, New York.**

Our knowledge of the functions of vitamins B and D in the animal economy is very scant. It was suggested by one of the present writers in 1913 that vitamin B plays a rôle in the metabolism of carbohydrates. This subject has been extensively reviewed elsewhere¹. In view of the criticisms of Vedder² it seemed advisable to repeat this work in a different way.

In the previous experiments, pigeons were fed forcibly various amounts of rice, and the time of the onset of beriberi determined. The experiments were also repeated with artificial food mixtures, the components of which were in various proportions. The results obtained at that time seemed to indicate that a higher proportion of carbohydrates precipitated the advent of the disease; however, the use of pigeons for this purpose is open to serious criticism, since these birds show an extraordinary facility in getting rid of food forced on them. While there seems to be no doubt that vitamin B has a marked relationship to the food intake, further proof being advanced in this paper, it is not easy to determine which constituent of the diet required the largest intake of vitamin B for its metabolism. Moreover, the natural foods rich in carbohydrates are usually low in proteins and vice versa. In bringing about beriberi the foodstuffs containing the largest amount of carbohydrates do not produce the disease on account of this factor, but rather because of the small amount of proteins they contain. This view was strengthened by the experience gained on rats, described in a fragmentary note in collaboration with Dubin³. Here we saw clearly that rats required more vitamin B, when fed a large proportion of carbohydrates than those receiving a large proportion of animal protein. The proteins used in these rat experiments had a

* The work was done under a grant given by Mr. Herman A. Metz to Columbia University.

very marked vitamine-sparing action, and this action was confirmed here on pigeons.

The experiments recently performed for the purpose stated above, did not yield a clear answer as to the rôle of vitamine B in metabolism, on account of practical difficulties encountered with pigeons, but they did show the vitamine-sparing action of proteins. They yielded also, improved and shortened methods for testing, biologically, fractions of vitamine B, with the ultimate view of isolating this substance. In addition to this, valuable information has been obtained regarding the vitamins actually required by pigeons for maintenance, together with data on the remarkable variations in the vitamine B requirements of individual pigeons.

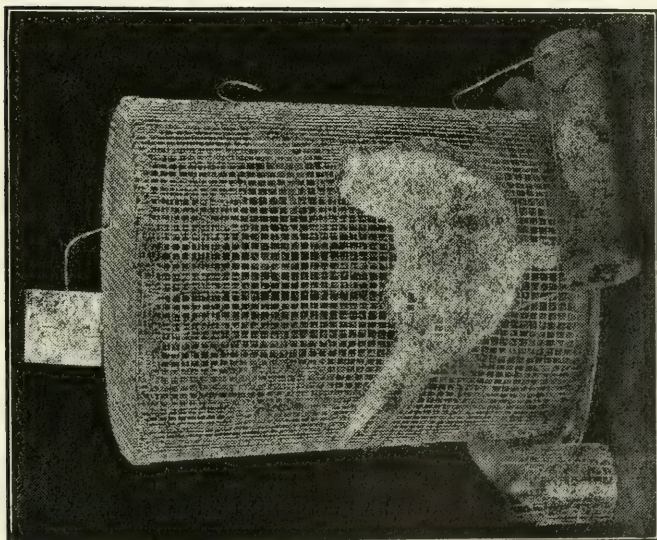
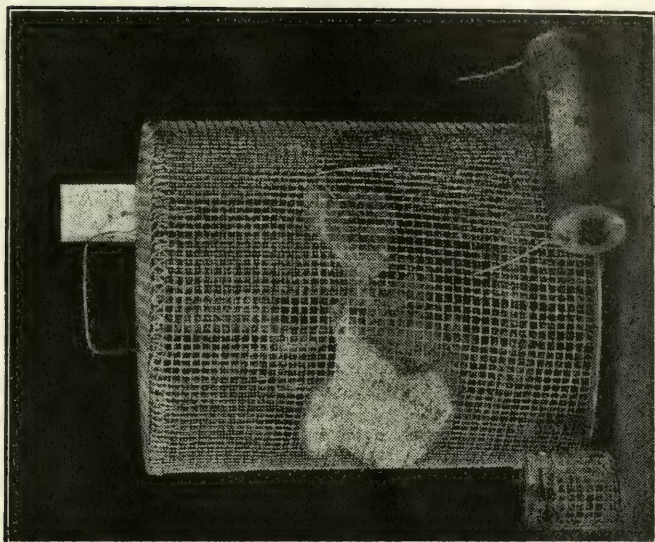
The second part of the paper deals with the experiments, by which the action of alkali and autoclaving on the stability of vitamins B and D was tested; also with the experiments used to determine whether microorganisms accidentally infecting the vitamine solution bear any relation to the gradual diminution of activity, which is often observed. These studies have led to an extremely interesting biological method for freeing the preparation of vitamine B, from the vitamine D, demonstrating that it is the D vitamine which promotes the growth of yeast.*

PART I.

RÔLE PLAYED BY VITAMINE B IN METABOLISM EXPERIMENTAL.

Some time ago the conclusion was reached that the present methods of testing vitamine B are so protracted as to render a chemical fractionation inexpedient. This is particularly true with the method using the curing of beriberi pigeons as a criterion. Even when a large number of pigeons are kept on a diet of polished rice, several may die without being used for an actual test and sometimes it is necessary to wait a long time until a sick pigeon is available, when a fraction is ready for testing. Moreover, when a number of birds are kept to-

* The above studies were only possible with vitamine preparations of constant activity, as the experiments were extended sometimes for a number of months. Such preparations made by Dr. Funk were placed at our disposal by Mr. H. A. Metz of the H. A. Metz Laboratories Inc., to whom we wish to extend our thanks. These vitamine preparations are referred to as M.V, M.VI and M.VII.



gether in one cage there are many disadvantages. Difficulty is encountered in keeping the cages clean, the weaker birds seldom have a chance to get at the food, and there is continual fighting. Furthermore, it is impossible to determine exactly the food intake of each bird, to study their behavior, the character of their excreta; and it is also difficult to prevent certain birds from devouring the excreta of others. This latter fact might cause serious mistakes when birds receiving vitamine and those receiving none are kept in the same cage.

The procedure finally adopted was as follows. Each bird was kept separately in a cylindrical cage, 12 inches high and 11 inches in diameter, made in the laboratory. These can be improved, by having a removable top and perhaps a food basket, which is placed on the outside, as in bird-cages, instead of on the inside of the cage. The cage stood upon a tin tray on which a few layers of newspaper were placed. These were changed every day and the spilled food collected and weighed back. After a few days and when the baskets were conveniently placed, the birds soon learned to eat rice without scattering it. The general arrangement can be seen from the appended photograph.

About every day the pigeons were taken out of the small cages and placed for a short time in large, clean stock cages where they could bathe and exercise a little. In all, one hundred pigeons were used, and the experiments covered a period of six and a half months. The weight of the birds and the food-intake was recorded every day but Sunday, and the special foods and vitamins were given daily. Since we began our work a similar method of testing vitamine B has been announced by Seidell⁴.

Experience teaches that with closer observation, individual control of food intake, and daily weighing of the birds, the time of testing can be shortened materially, particularly if a sufficient number of pigeons are used. A group of six birds is now generally used, with a known vitamine requirement, and it can be determined in four or five days whether or not a fraction contains vitamine B. It is only very rarely that we have to extend the time of testing. During these few days the dose may even be varied so as to determine the minimum dose necessary for a given vitamine solution.

By using individual cages, it has been noted that sometimes unchanged food is excreted in the feces, which shows that not all food ingested is metabolized. This observation, of course, complicates the study of the influence of various food constituents. In dealing with the individual pigeons the enormous variations in the food requirements and vitamine requirements of the individual birds were also observed. This fact is discussed in another connection.

It can be seen from Chart I, which is a composite curve for six pigeons, covering a period of two hundred days, during which some thirty fractions containing B vitamine, and others devoid of it were

tested, that this method yields reliable results. When an active fraction was administered to the birds there was an immediate rise in the weight curve, and a corresponding fall when the fraction was inactive. So perfectly do these fluctuations indicate the nature of the vitamine fraction given, that it is not necessary to mark the periods on the chart. By using subsequent fractions from the same initial material the result of previous tests was always confirmed, showing the reliability of this method.

The marked variations obtained with fractions tested show that testing them on pigeons from four to five days is fully sufficient to determine the completeness of chemical fractionation.

This is perhaps the first time that pigeons have been kept over a half year on polished rice plus a *highly purified* B vitamine. It corroborates an earlier suggestion of one of the authors⁵, and shows that adult pigeons (experiments on young pigeons are described later) need only vitamine B and can dispense with others. The fractions used were all purified fractions of vitamine B, practically devoid of vitamine D and A.

Before starting these tests a sufficient quantity of vitamine B was prepared to last throughout the entire experiment, thus securing a vitamine of constant activity, and preventing errors due to variations in the preparations.

It can be seen that the virility of the adult birds was not seriously impaired by the prolonged feeding on polished rice, for, within a week after they were put back on normal diet, several females laid eggs, and three normal young birds were hatched within six weeks.

For reasons already published with Dubin⁶ and confirmed in our present work, the rat is not considered suitable for testing this substance, on account of its more complicated requirements in vitamines. The rat serves well the purpose when natural foods are tested for vitamine B, plus the other nutritive factors which regularly accompany this vitamine, but fails partially where purified vitamine B, devoid of vitamine D and perhaps other vitamine, is administered. This may be considered a reply to the assertion made recently by Levine, McCollum and Simmonds⁷, who state that pigeons are unsuitable for testing B vitamine. Nevertheless, a number of parallel experiments on rats were made, with the same preparations used for pigeons. Here also the effect was prompt, the food intake rose and the growth was resumed, but the effect was

of a smaller magnitude than when vitamine B in natural form (yeast) was given. Here, as with pigeons, we came to the conclusion that by using rats which declined on account of deficiency in vitamine B, the period of testing need not be extended beyond ten, or possibly fourteen days. If, in this time, the effect is insignificant, one may safely conclude that the fraction is devoid of or deficient in vitamine B. The rôle of B vitamine and the question of other vitamines of this type playing a part in the metabolism of this animal, will be treated in a subsequent communication.

THE INFLUENCE OF CARBOHYDRATE AND PROTEINS ON THE REQUIREMENTS OF PIGEONS IN VITAMINE B

In a preliminary experiment which will not be described in detail, three groups of six pigeons each were fed with a mixture of dextrose and egg-albumin in various proportions. The experiment failed, as a number of birds died on account of the crop being closed by the difference in osmotic pressure of the sugar solution and the body fluid. The experiment was then arranged in a different way. Eight pigeons were placed in the cages previously described, and fed polished rice. A vitamine preparation (M.V) was given every day and the dose increased or diminished until the birds neither gained nor lost weight. It was expected that by introducing forcibly a known quantity of starch, the vitamine requirements would be increased, as compared with the first period, and that further the vitamine would have to be increased with every increased dosage of starch. On the other hand, it was supposed that the vitamine requirements of pigeons, to which a solution of egg-albumin or other protein was added, would diminish. As a control we kept birds which received varied and increasing amounts of a well-balanced diet. This means casein, starch and salts.

The first of these experiments did not turn out as expected: as soon as starch suspension was forced upon the birds, they stopped eating rice and lived remarkably long without much loss in weight on this food, so poor in nitrogen. All efforts to make them eat rice again failed, and particularly increasing the amount of B vitamine was of no avail. As indicated in Chart II, the rice intake increased, however, when the amount of starch was diminished and a small proportion of casein and

salt mixture added. Evidently 5 grams is the optimum allowance, because when the proportion of starch was increased in the mixture, the rice intake fell off, and stopped entirely when the starch was increased to nine-tenths of the mixture. Even a larger dose of vitamine B did not increase the rice intake. As the administration of this diet necessitated the introduction of considerable water, a set of control birds were given the same amount of water in addition to their voluntary intake. This forced water-feeding did not interfere with either their weight or rice intake.

TABLE I.

Comparison of the weights of eight pigeons during the entire experimental period (grams.)

No. of Pigeon	Weight as purchased Dec. 29	Weight at beginning of special period Feb. 4	Weight when starch-feeding was started Feb. 22	Loss or gain since date of purchase	Final Weight	Final weight compared with weight Feb. 4	No-vitamine period, before beriberi
224	370	303	340	-30	289	95%	14 days
225	341	272	303	-38	266	97%	14 "
221	269	278	285	+16	272	97%	14 "
227	336	281	319	-17	271	96%	18 "
202	366	252	277	-89	237	94%	18 "
241	296	284	311	+15	242	85%	22 "
247	237	247	272	+35	234	94%	22 "
226	300	290	305	+ 5	165	57%	33 "

TABLE II.

Comparison of weight and rice-intake on maintenance vitamine requirement (grams).

No. of pigeon	Average rice-intake per day Feb. 4-22	Average weight Feb. 4-22	Rice intake in terms of body weight	Vitamine requirements per day, c.c.
224	22	320	1/14	0.8
225	16.6	288	1/17	0.8
221	21	293	1/14	1.2
227	21	299	1/14	1.0
202	18.6	265	1/14	0.8
241	17	298	1/17	1.0
247	14	251	1/17	1.0
226	18	296	1/16	0.8

TABLE III.

Comparison of weight and rice-intake on high vitamine requirement and no vitamine.

PERIOD OF LOW STARCH FEEDING AND HIGH VITAMINE.					PERIOD OF NO VITAMINE DIET, RICE ONLY.			
Diet, 5 gms. starch / Vitamine, M.V.2.5-2.7 cc. 2.5 " casein / fed 0.5 " salts / rice, voluntary intake								
No. of pigeon	Average		Average food intake 8 gms. diet plus rice	Food intake in terms of body-weight	Average		Rice intake in terms of bodyweight	Time before beriberi
	Weight	Rice intake Mar. 12-29			Weight	Rice intake April 22-May 5 and f.f.		
224	315	10	18	1/17	308	10.9	1.28	14 days
225	310	13	21	1/14	293	13	1.22	14 "
221	291	17	25	1/11	302	14.9	1.22	14 "
227	308	8	16	1/19	301	8	1.37	18 "
202	284	12	20	1/14	277	9	1.30	18 "
241	283	10	18	1/15	272	9	1.30	22 "
247	276	12	20	1/13	276	10	1.27	22 "
226	277	10	18	1/15	222	7.7	1.28	33 "

The experiment was then repeated without the use of rice, by giving to the birds a mixture of casein, salts and starch, the first and second ingredient being kept constant, only the amount of starch being varied. Here the difficulty consisted in the administration of a sufficiently large amount of starch. The attempt had to be abandoned, when the food mixture was vomited and the amount ingested could not be controlled. The value of the experiments was also diminished by the fact that in both experiments considerable amounts of unchanged starch found its way into the feces.

The results of the experiment in which the amounts of casein, starch, and salts were well balanced are shown in Chart III. Increasing the amount of vitamine over the necessary amount (1 c.c.) did not increase either the body weight or the rice-intake. In the period without rice, using a mixture of casein, starch, sugar and salts (a slightly higher proportion of protein as compared with rice) the body weight rose on a just sufficient amount of vitamine B.

We were more fortunate with the protein experiment. Here, as in the starch experiment, we started with birds in vitamine balance and then added egg albumen raw in liquid form. This addition has a distinct vitamine-sparing influence and the daily vitamine dose could be very materially reduced. The

experience here gained (Chart IV) is in perfect accord with the results published with Dubin on rats, and is in distinct disagreement with the statement of Vedder⁸ who asserts that *starch* addition delays the onset of beriberi. In reality his earlier experiments with sterized meat or egg (Vedder²) in contradiction to his recent statement, show the same vitamine-sparing action as do the results obtained by the authors. (See also the experiment on young pigeons and Chart XIV).

Although egg-white is known to be free from vitamine B, we performed the usual control experiment with egg-albumen alone, using three birds. Here the characteristic initial loss of weight, usually observed on a vitamine-free diet of polished rice, was delayed, but finally all the birds developed the disease (Chart V). We tried to obtain further data by using casein and other proteins. We were also particularly interested in discovering whether there was any difference between the proteins of animal and plant origin in their vitamine-sparing action. Here, however, we were hampered on account of the uncertainty of the vitamine-freedom of the commercial preparations and lack of time to prepare them ourselves. From the animal proteins, we attempted experiments with gelatin in solution, specially purified casein and a solution of casein, hydrolyzed with sulphuric acid and carefully neutralized with baryta. We had difficulty in giving these preparations to the pigeons and the attempts had to be abandoned.

It seems unlikely that the sparing influence of the protein products should be explained by the action of vitamine B contained therein, but rather by a specific action of the protein. This invites further investigation. Our subsequent experiments will clearly show the dependence and close relationship between the intake of polished rice and the vitamine requirements of the birds. However, we must admit that our contention that the B vitamine is particularly concerned with starch-metabolism, does not rest for the present on a sound experimental basis and will have to be modified, perhaps, in the sense suggested before, viz., that the relationship between high protein and vitamine requirement is also an important factor. We have already mentioned that diets low in protein are usually high in carbohydrates. We have endeavored to test our earlier contention regarding relationship of the rapidity

with which beriberi develops and the amount of rice consumed. This experiment performed on pigeons kept without vitamin addition and voluntary rice-intake is described later in this paper.

LOW VITAMINE INTAKE AS COMPARED WITH NO VITAMINE INTAKE.

It was thought possible that an insufficient administration of vitamin, on account of stimulation of the metabolism, would produce beriberi earlier than when this addition is omitted. Consequently we placed six pigeons on polished rice with an addition of 0.4 cc. of M.VI, of which normally about 1.5 cc. were required, and we had six controls without vitamin. As Chart VI shows, the birds kept on a diet without vitamin developed beriberi, while the others were in fairly good condition.

VARIATIONS IN THE REQUIREMENTS FOR VITAMINE B IN INDIVIDUAL PIGEONS.

In testing fractions of vitamin B on pigeons, we have repeatedly noticed that when the dose was kept constant, some pigeons gained, some maintained, and some lost weight. We have frequently observed that male pigeons showed a higher rice consumption than females, but we do not as yet possess sufficient data to show to what factor this variation is due. It seems to be independent of the weight of the animal and the exact influence of sex, age and breed still remains a problem to be investigated.

This finding is no doubt of practical importance for testing B vitamin on pigeons. In testing the potency of commercial vitamin preparations, Hess, Moore and Calvin⁹ have used a very small number of pigeons with probably a variable requirement. It seems in the light of our studies, that to make a reliable test, either a large number of pigeons have to be used, or pigeons with a known vitamin requirement.

The experiment was arranged so that fourteen pigeons of different size, sex, and weight were used, just as supplied by the dealer. One of the birds died early and had to be replaced by pigeon 201. The weights of the pigeons ranged between 452 and 298 gm. All birds were started on polished rice and 1 cc. of M.VII preparation. To determine the minimum vitamin requirement the birds were allowed to lose weight

on an insufficient dose of vitamine. The dosage was then increased until the weight loss was stopped and this final weight maintained without further gain, or with but very slight daily variations. It was soon evident that for a few birds the dose could be diminished, while in most of them it had to be considerably increased. The experiment has shown that the B vitamine requirements are practically independent of the weight of the birds. A larger vitamine requirement causes larger intake of polished rice; in short, food intake is dependent on the vitamine required. This was particularly in evidence when the birds were divided into three groups; low, medium and high vitamine requirement. The intake of polished rice increased with the increase in vitamine requirement, but if daily body weight was divided by the amount of food intake for that same day, it was found that the average food intake for all three groups was one twenty-eighth of the body weight. This represents the food requirements in terms of polished rice, when the animals received just enough vitamine to be kept in equilibrium; this amounts to ten or twelve grams per day, a surprisingly small amount.

In the series of eight pigeons used for the starch-feeding experiment, the rice intake was much higher during the corresponding preliminary period when they received only rice and vitamine B. (See Tables I and II). This was due to the following reasons. First, the birds received a maintenance allowance of vitamine, slightly more than the minimum requirement, as shown by the fact that in the end some of the birds gained in weight. It was found on further testing that the M.V vitamine preparation used for this series was slightly more active than the M.VII used for the fourteen pigeons.

These differences in the vitamine and food requirements of pigeons may throw light upon the variations observed by clinicians in deficiency diseases in various individuals on apparently the same diet.

It can also be observed from the average curve in Chart VII and the group Charts VIII, IX and X that with the initial falling of body weight, the food intake gradually came down until equilibrium was established, then, the daily variations in the food intake became very great; usually, a day of high food intake was followed by a day of exceedingly low consumption. It would be interesting to show the individual curves for the pig-

eons, but we have to omit them for the sake of saving space. The vitamine B requirement of these animals varied from 0.09 cc. to 2 cc. per day, and it is possible that still wider variations could have been obtained. That we had an equilibrium can be seen from other experiments performed on the same birds with identical vitamine dosage, which has been maintained from April 4th until June 2nd — quite a long time.

EXPERIMENT WITH YOUNG PIGEONS.

An experiment was made with nine young pigeons to see whether their vitamine requirement was the same as that for adult pigeons, and to determine what should be added to the polished rice to supplement its deficiency and promote growth.

One of the young pigeons was sixty-eight days old, four were forty-eight, three forty-seven, and one forty-five days old.

The birds were fed polished rice for two months. At first the dose of vitamine (M.VI) was 1 cc., but at intervals of five days this was increased by 0.5 cc. up to 3 cc.

When they showed a slight loss in weight on the twentieth day, a series of trials were made to try to supply the lack. They were given successively for periods of five days, (1) 2 cc. of carrot juice, (2) 1 gm. of casein, (3) 10 cc. of raw egg albumen, (4) 10 cc. of egg albumen plus 0.25 gm. of calcium lactate and 0.25 gm. of potassium phosphate. Then, since they seemed to do best on the egg-albumen alone, the two salts were omitted for ten days, and finally for a period of five days they were fed 10 cc. of egg-albumen plus 0.14 gm. of the salt mixture used in synthetic rat food (Osborne-Mendel formula). Two of the young birds became sick with a condition similar to that which Abderhalden calls "pigeon diphtheria" and had to be taken off the experiment at the end of thirty-five and thirty-seven days respectively. The other seven birds were maintained but only gained slightly in weight (Chart XIV). The greatest gain in weight was during the periods of feeding egg-albumen without the addition of salts. During the period of feeding salts some of the birds had diarrhea, and although there was no marked loss in weight they did not seem as well and lively during this diet period.

STORAGE OF B VITAMINE.

In giving on Saturday a double dose to last for two days, we have almost constantly observed (Chart I), where pigeons were kept for two hundred days, that the pigeons lost weight, except in a few cases, where a considerable over-dose was given, while the same dose given in two equal daily portions was fully adequate. A few experiments to test this point convinced us soon that this was not so much a question of storage as the question of food intake. It can readily be seen (Table IV) that, with a double dose, the food intake the first day is much larger than that on the second day, while with single doses the food intake happened to be larger on the second day. The weights of the birds varied accordingly, the first group lost weight, the second group maintained its weight.

TABLE IV.

<i>Double Dose</i>				
Average weight	Weight next day	Food Intake	Weight 2nd day	Food Intake
308	310	14	296	9
<i>Single Doses</i>				
278	278	9.5	278	12

This experiment was repeated with the same result on a few more occasions.

That the vitamine storage plays a part can be seen from the next experiment where vitamine was discontinued and beriberi produced. The experiment was planned primarily to see whether when the outbreak of beriberi is prompt, it is connected with a large intake of polished rice. The voluntary rice intake, however, was very small in all cases and the variations between the individual birds insignificant as Table V shows. But what was striking is the rapidity with which beriberi developed. Whereas in normal pigeons the disease occurs after twenty to thirty-five days of rice feeding, here out of fourteen birds:

1	became sick on the	7th day
1	" " " "	8th "
4	" " " "	9th "
5	" " " "	10th "
2	" " " "	13th "
1	was normal for more than 30 days.	

After nine to ten days there was an epidemic as it were,

nine birds succumbing within these two days. The rapidity of the onset was probably due to the fact that the birds received only enough vitamine B to keep in weight equilibrium and had but a small amount of it stored. If the first two pigeons, which developed the disease after seven and eight days respectively, and behaved rather abnormally, are disregarded, and the others are divided into groups according to the quickness of the development of the disease, then the food intake, on the average, ran as follows:

	Before the experiment	After discontinuation of vitamine
9 days	12.4	4.0
10 "	10.4	2.9
13 "	10.3	1.7

We see from these figures that the general trend of the experiment ran as we expected, although more birds would have been desirable. It would be interesting to learn the reason for the prolonged resistance of pigeons 392. It was the largest pigeon of all and stopped eating entirely, so that after a certain time hand-feeding had to be resorted to. It did not develop beriberi even after thirty days, in spite of great loss

TABLE V.

Food intake and time of development of beriberi.

PRELIMINARY PERIOD						NO VITAMINE PERIOD				
Pigeon	Vitamine requirement* c. c.	Initial Weight	Final Weight	Food Intake	Per day	Initial Weight	Final Weight	Food Intake	Per day	Beriberi days
389	1.1	253	261	43	10.8	256	221	13	1.85	7
201	2.0	195	300	41	10.2	304	261	29	3.6	8
393	1.8	289	302	63	15.7	298	247	17	1.9	9
394	1.4	293	293	45	11.2	295	270	53	5.9	9
378	0.9	250	258	27	6.7	253	223	23	2.5	9
379	1.0	195	202	63	15.7	217	187	51	5.6	9
395	1.3	266	273	44	11	279	231	24	2.4	10
385	1.8	296	302	54	13.5	294	265	33	3.3	10
384	1.7	305	307	39	9.7	299	263	19	1.9	10
377	1.8	248	254	34	8.5	254	208	31	3.1	10
380	1.3	236	237	37	9.2	233	205	38	3.8	10
366	1.2	286	292	49	12.2	292	218	26	2.0	13
381	1.5	295	296	34	8.5	291	239	18	1.4	13
392	1.8	360	370	51	12.7	370	248			No beriberi after 30 days

* For the meaning of the term vitamine requirement see page 747.

in weight. After twenty days, hand-feeding was started and loss in weight checked. When the same experiment was made with pigeons in vitamine equilibrium the results in Table V were obtained. (Compare with Tables I, II and III).

PART II.

ACTION OF ALKALI, HIGH TEMPERATURE AND CONTAMINATION ON B VITAMINE, TOGETHER WITH SOME REMARKS ON VITAMINE D.

Having at our disposal fourteen birds with a known vitamine requirement, we decided to utilize them for the purpose mentioned here in the title. First we were interested to see whether a microorganism like yeast, or some other fungus, takes the B vitamine out of the solution for purposes of nutrition. During the chemical fractionation the fractions stand for a long time, usually without an addition of antiseptics, and therefore it is of practical importance to determine this point. The question has gained in interest since a paper of Eijkman, van Hoogenhuijze and Derks¹⁰ appeared. These authors came to the conclusion that yeast takes B vitamine out of a solution and renders it inactive for fowls fed on polished rice. Yeast grown on a synthetic medium was also found devoid of vitamine B. But as Nelson, Fulmer and Cessna¹¹ have found that yeast grown in such a manner contains the B vitamine necessary for rats, Eijkman and collaborators came to the conclusion that the vitamine necessary for fowls and rats are two different substances.

This observation of Eijkman, however, is not in harmony with the finding of Wildiers¹² who found in 1901 that the yeast growth-promoting substance, now called vitamine D, is taken out during the multiplication of new yeast cells. This fact has recently been confirmed by Clark¹³. He stated that yeast takes out the growth-promoting substance after three hours of incubation. The work set forth herein was started prior to the appearance of Clark's paper and means a substantial advance, as the problem was attacked from the point of view of presence of at least two vitamines in yeast. The results have shown that yeast, or some other fungus, grown under the conditions of the experiment on a mixture of B vitamine with a small admixture of D vitamine, takes the latter out of solution, but leaves the vitamine B intact. These experiments were then extended to

see how long it takes to remove the D vitamine from solution. The elimination of D vitamine by growing yeast was tested on rats (see Chart XII) as well as on pigeons and no difference in behavior could be observed, as suggested by Eijkman, Hoogenhuijze and Derks¹⁰.

With the pigeons in vitamine equilibrium two more experiments were performed. Both experiments are of great practical importance for the isolation of B vitamine, and by using the method described, the problem was solved. The first of these experiments dealt with the destructive influence of alkali, an assertion which could be fully confirmed. The second experiment dealt with the influence of autoclaving on the stability of B vitamine. The second of these experiments has a distinct bearing on the influence of canning on the vitamine B content of foods and gives repeated evidence that B vitamine can stand repeated autoclaving for ten pounds pressure for ten minutes, but that higher temperatures and longer heating have a very unfavorable influence. The influence of alkali and of autoclaving is very similar in its action on the D vitamine, but the vitamine D appears to be somewhat more stable. This is the first time that such experiments have been performed on pigeons given a minimal dose of vitamine B.

EXPERIMENTAL

I.

THE INFLUENCE OF YEAST GROWTH ON A SOLUTION OF B AND D VITAMINES.

For all the next pigeon experiments, our fourteen pigeons, maintained on their minimum vitamine B requirements, were divided into two groups of seven pigeons each, one group serving as a control. All the experiments described in the introduction to Part II are plotted on the same Chart XI together with the food intake which serves as a control to the weight curve.

For the first experiment 2.64 gm. of M.VII preparation of vitamine B were dissolved in 400 cc. of Nægeli solution and this divided into two portions. Both solutions were sterilized for ten minutes at ten pounds pressure. One solution was inoculated from a yeast culture and incubated for 48 hours at 30°. The growth was not copious, due to lack of D. Both solutions

were heated to 80°, then filtered, put into test tubes in amounts each sufficient for one day's dose and sterilized for ten minutes at ten pounds. The dose for each pigeon was exactly the same as in the preliminary period.

The same solutions were also given to two series of rats, kept on a diet free from B vitamine. The result of the yeast-growth tests, method described by Funk and Dubin¹⁴, have shown that the solution on which yeast was grown was entirely free from D vitamine, while our experiments on pigeons and rats (especially the first) have shown that the B vitamine was left intact by the yeast which developed in it, the control animals behaving exactly the same as the experimental ones.* The behavior of the rats is shown on Chart XII.

The results on the two days following these experiments show the effect of two single doses on successive days, as compared with one double dose, given on one day, described in this paper. Group I received a double dose; Group II, two single doses in two days.

II.

THE INFLUENCE OF CONTAMINATION FROM THE AIR ON THE ACTIVITY OF B AND D VITAMINES.

In this experiment the influence of germs in the air was studied, since this has a special bearing on the chemical isolation of these vitamins. 1.32 gm. of M.VII were dissolved in 200 cc. of Nægeli solution, divided into two parts and sterilized in Erlenmeyer flasks for ten minutes at ten pounds pressure. One Erlenmeyer was then opened and left open for one hour, then plugged and both solutions kept in an incubator for five days at 30°. At that time the surface of the liquid in one Erlenmeyer was covered with a profuse growth of *Mucor mucedo*, the dried mycelium amounting to two gm. Both solutions were heated to 80°, filtered into individual test tubes and sterilized again at ten pounds for ten minutes. The contaminated solution was much deeper in color. On Chart XIII the first group represents the control, the second the contaminated solution. The result of the yeast-growth test showed that the D vitamine was almost eliminated from the solution.

* These yeast-growth tests were made for us by Louis Freedman, to whom our thanks are due.

Solution	Quantity of yeast cells measured in mm.	Net gain
Contaminated.....	4.5 mm.	1.0 mm.
Control	8.5 "	5.5 "
Blank	3.5 "	—

III.

THE INFLUENCE OF ALKALI ON THE B AND D VITAMINES.

1.32 gm. of M.VII were dissolved in 100 cc. of water and divided into two portions which were sterilized at ten pounds for ten minutes. To one portion were added, with a sterile pipette, 20 cc. of N NaOH and immediately afterwards 20 cc. of sterile N HCl. To the other portion were added 20 cc. of the same alkali and, after four days' standing, 20 cc. of the acid. The liquid was then distributed into test tubes and re-sterilized. The first group of pigeons received the alkalinized solution. The result of the pigeon experiment (Chart XI) indicates that the B vitamine was destroyed to a very large degree if not completely, while the result of the yeast test showed that the D vitamine had been only slightly affected.

Solution	Quantity of yeast cells measured in mm.	Net gain
Alkali	6.0 mm.	2.5 mm.
Neutral	8.0 "	2.5 "
Blank	3.5 "	—

IV.

THE INFLUENCE OF AUTOCLAVING ON THE ACTIVITY OF
B AND D VITAMINES.

The following experiment illustrates very well the time factor in the inactivation of vitamins of the B type. We have said already that autoclaving for ten minutes at ten pounds pressure does not seem to produce any detectable decomposition of the vitamins B and D. Here 1.32 gm. of M.VII were dissolved in 200 cc. of water, and divided into two portions. One portion was sterilized for one hour at twenty pounds, the other for three hours at twenty-five pounds. The first group of pigeons received the solution heated for one hour at low pressure, the second group the one heated for three hours. The latter proved to be almost devoid of B vitamine, while the action on D vitamine was of the same order, but somewhat

less marked, showing perhaps that D vitamine is more resistant than B. See Chart XI.

D VITAMINE RESULTS.

Solution	Yeast growth in mm.	Net gain
Short autoclaving.....	7.0 mm.	3.5 mm.
Long ".....	6.0 "	2.5 "
Blank	3.5 "	—

STUDY OF YEAST GROWTH IN ITS ACTION ON THE D VITAMINE.

The experiments described below, deal with our first attempts to study the conditions under which the D vitamine is taken out of solution by the growing yeast cell. While our results tended in general to show that the amount of this vitamine diminished when yeast or a similar microorganism was grown in solution, the disappearance of this vitamine was not quantitative under all conditions. Apparently the presence of inhibitory substances, as those in autolyzed yeast, have an unfavorable influence on this biological reaction. For the time being our preliminary results tend to show that the most favorable conditions for the separation of B and D are an active and as pure as possible vitamine B (such as we have employed), containing only a small admixture of vitamine D. Under such conditions we have repeatedly noted a complete disappearance of vitamine D, leaving the vitamine B quantitatively in the solution. All our experiments so far were made with a Nägeli solution, which is a distinct disadvantage from the point of view of chemical fractionation, introducing sugar and a number of inorganic salts as a nutritive medium. But in spite of the disadvantage of the solution so far nothing more suitable has been found. It is proposed also to ascertain how the growth of yeast influences the composition of the more or less crude vitamine fractions. It is to be hoped that by starting from a vitamine preparation containing the vitamines B and D, and growing yeast on it, the vitamine D and other impurities, may be completely eliminated having been utilized by the yeast cell and filtered off with the latter.

Our present results show, to our great surprise, that not only does the yeast cell take the vitamine D out of the solution, but keeps it tenaciously for at least 88 hours, the longest time, we have extended our experiments. On warming the yeast suspension above the coagulation temperature of the proteins,

and filtering the yeast through an ordinary folded filter, the resulting filtrate, when clear, was found to be free from vitamine D. The affinity therefore, of the yeast cell for this vitamine must be very great for as soon as a cell autolyzes and yields its contents to the solution, the liberated vitamine D is apparently immediately captured by the living cells. The experiments do not, for the present, corroborate the assertion of Robertson¹⁵ in regard to protozoa, namely, that these micro-organisms, while growing, give out some substance to the nutritive medium, which permits the growth of other similar protozoa. This does not seem to be case with the yeast cell.

The preliminary experiments deal with the influence of concentration of the vitamine fraction; the difference in behavior of autolyzed yeast as compared with a greatly purified fraction; the behavior of a preparation of D vitamine free from B vitamine; and studies on the time of incubation necessary for a complete disappearance of vitamine D from the solution. Present results tend to show that about 48 hours' incubation at 30° seems to be the best under existing conditions.

VITAMINE B PREPARATIONS SHOWN BY THE YEAST TEST TO
CONTAIN SMALL QUANTITIES OF D. EXPERIMENT I.

132 mg. of M.VII was dissolved in 20 cc. of Nägeli solution and divided in four test tubes. Two test tubes were inoculated with a pure culture of yeast grown on malt agar for 48 hours. One test tube with Nägeli solution was inoculated in the same way, the other two tubes were kept as controls. All the solutions were tested in two concentrations (1 and 0.5 cc.) using our usual technique. When the culture was 48 hours old, the tubes were heated to kill the yeast and filtered. It could be seen with the naked eye that the vitamine solutions gave more abundant growth than Nägeli solution alone. The result obtained from the yeast test with the filtrates were as follows:

Nature of solution			Yeast growth in mm.	Net yeast growth
1	M.VII sol. inoculat.	1 cc.....	2.0	0
2	" " "	0.5 " first tube....	2.0	0
3	" " "	1 " " ".....	2.0	0
4	" " "	0.5 " second tube...	2.0	0
5	" control sterile	1 " first tube....	4.5	2.5
6	" " "	0.5 " " ".....	4.0	2.0
7	" " "	1 " " ".....	4.5	2.5
8	" " "	0.5 " second tube...	4.5	2.0
9	Nägeli inoculated	1 "	2.0	0
10	" " "	"	2.0	0
11	Blank: yeast without vitamine D.....		2.0	—

In this experiment vitamine D was completely taken out, while when grown in Nägeli solution no vitamine D is given out by the yeast.

EXPERIMENT II.

In this experiment the procedure was repeated by using autolyzed yeast in various dilutions. The concentrations first used were autolyzed yeast diluted twice, ten and twenty times. One half the number of tubes were inoculated, the other half kept as controls. All samples were heated, filtered and the yeast-test made with the filtrates. As the yeast grew poorly, the experiment was not very conclusive, probably on account of inhibitory substances.

SOLUTIONS				Volume of solution used	Quant. of yeast cells measured in mm.	Reading minus the blank
1.	Autol. yeast	sterile	1/2 conc.	1 cc.	16	12.5 mm.
2.	"	"	inoc. 1/2	"	19	15.5 "
3.	"	"	sterile 1/2	" 0.5	11	7.5 "
4.	"	"	inoc. 1/2	"	11	7.5 "
5.	"	"	sterile 1/10	" 1	5.5	2.0 "
6.	"	"	inoc. 1/10	"	6.0	2.5 "
7.	"	"	sterile 1/20	"	5.5	2.0 "
8.	"	"	inoc. 1/20	"	4.5	1.0 "
9.	Blank			"	3.5	—

The experiment was repeated with more dilute solutions of autolyzed yeast counting on less inhibitory action in lower concentrations. The concentrations chosen were 1/20, 1/25, and 1/30. The tube 1/25 gave poor growth.

SOLUTIONS				Volume used	Quant. of yeast cells measured in mm.	Reading minus the blank
1.	Autol. yeast	sterile	1/20	1 cc. used	5.5	2.0
2.	"	"	inoc. 1/20	throughout	6.0	2.5
3.	"	"	sterile 1/25	"	4.5	1.0
4.	"	"	inoc. 1/25	"	4.5	1.0
5.	"	"	sterile 1/30	"	4.0	.5
6.	"	"	inoc. 1/30	"	3.5	0
7.	Blank			"	3.5	

Apparently on account of inhibitory substances present, results are irregular and become similar to purified vitamine solutions in only very low concentrations.

EXPERIMENT III.

In this experiment the influence of the vitamine concentration was tested, by varying the amount of vitamine and Nägeli solution in each tube. Two different vitamine preparations were tested, M.VI and M.VII. The vitamine solutions were incubated at 30° for twenty hours only, which does not seem to be sufficient in all cases. M.VII was tested in five concentrations and M.VI in two. The concentration of the original vitamine solutions was 1.32 gm. in 40 cc. Nägeli.

CONCENTRATION OF SOLUTIONS TESTED	Quant. of yeast cells measured in mm.	Reading minus the blank
1. 5cc. M.VII sterile.....	15	11.5
2. " inoc.....	10	6.5
3. 4cc. + 1cc. Nägeli sterile.....	12	8.5
4. " inoc.....	8	4.5
5. 3cc. + 2cc. " sterile.....	10.5	7.0
6. " inoc.....	6.5	3.0
7. 2cc. + 3cc. " sterile.....	10.0	6.5
8. " inoc.....	5.0	1.5
9. 1cc. + 4cc. " sterile.....	9.0	5.5
10. " inoc.....	4.0	.5
11. 5cc. M.VI " sterile.....	8.0	4.5
12. " inoc.....	6.5	3.0
13. 2.5cc. M.VI + 2.5 Nägeli sterile.....	7.5	4.0
14. " inoc.....	5.5	2.0
15. 5cc. Nägeli inoc.....	3.5	0
16. Blank	3.5	
17. "	3.5	

This experiment suggests strongly that for the removal of D vitamine from solutions, higher dilutions are more favorable.

EXPERIMENT IV.

This experiment was performed to study the influence of the length of time of the incubation. The vitamine preparation used was M.VII. An inoculated solution and a sterile control, together with an inoculated Nägeli solution, were kept in an incubator and at intervals of twenty-two hours samples taken out in a sterile way, heated and filtered. With the filtrates the yeast test was made. Both vitamine solutions were tested for the D vitamine content before inoculation. As the yeast hardly grew at all for the first forty-four hours, the vitamine D was not taken out in the first two time intervals.

CONCENTRATION OF SOLUTIONS TESTED		Quant. of yeast cells measured in mm.	Reading minus the blank
1. Sol. I	before inocul.	8.5	5.0
2. " II	" "	8.5	5.0
3. Sol. I	sterile 22 hours	8.5	5.0
4. " II	inoc. " "	8.5	5.0
5. Nägeli	inoc. " "	3.5	0
6. Sol. I	sterile 44 "	8.5	5.0
7. " II	inoc. " "	8.5	5.0
8. Nägeli	inoc. " "	3.5	0
9. Sol. I	sterile 66 "	8.5	5.0
10. " II	inoc. " "	7.0	3.5
11. Nägeli	inoc. " "	3.5	0
12. Sol. I	sterile 88 "	8.5	5.0
13. " II	inoc. " "	5.5	2.0
14. Nägeli	inoc. " "	3.5	0
15. Blank	3.5	
16. " "	3.5	

EXPERIMENT V.

This last experiment was performed with a solution of vitamine D, obtained from yeast and completely freed from vitamine B by fractionation. In order to avoid contamination in taking our samples the solutions were divided into portions at the beginning and taken out of the incubator after a certain interval of time, together with the controls. On account of inhibitory substances the yeast growth was slow in starting. It was noticed that the solution of D vitamine was cloudy on autoclaving but became clear on cooling. After the yeast growth started on it this phenomenon disappeared, suggesting that some substances were utilized by the yeast cell during

CONCENTRATION OF SOLUTIONS TESTED		Quant. of yeast cells measured in mm.	Reading minus the blank
1. Sol. I	8.5	5.5
2. " II	before inoculat.	8.5	5.5
3. Nägeli	" "	3.0	0
4. Sol. I	sterile 24 hours	8.5	5.5
5. " II	inoc. " "	8.5	5.5
6. Nägeli	inoc. " "	3.0	0
7. Sol. I	sterile 48 "	8.5	5.5
8. " II	inoc. " "	7.5	4.5
9. Nägeli	inoc. " "	3.0	0
10. Sol. I	sterile 60 "	8.5	5.5
11. " II	inoc. " "	6.5	3.5
12. Nägeli	inoc. " "	3.0	0
13. Sol. I	sterile 72 "	8.5	5.5
14. " II	inoc. " "	5.0	2.0
15. Nägeli	inoc. " "	3.0	0
16. Blank	3.0	
17. " "	3.0	

its development. This cloudiness disappeared only after forty-eight hours coinciding with the growth of the yeast and the diminution of the D vitamine in solution.

The studies on the biological separation of vitamine D from vitamine B are being continued by us. We wish to thank Dr. William J. Gies for many facilities placed at our disposal in connection with the work.

SUMMARY

1. Pigeons are more suitable for testing vitamine B than rats, because of the complicated vitamine requirements of the latter.

2. A short procedure is described for testing vitamine B on pigeons.

3. Further evidence is presented on the vitamine-sparing action of certain proteins known to be free from vitamine B.

4. Increased carbohydrate feeding did not give a clear result as regards an increased vitamine requirement.

5. Increasing the amount of vitamine B did not increase the intake of a well balanced diet.

6. Individual pigeons show great variations in their requirement of vitamine B. The birds with large requirements had a greater average intake of rice. This variability of vitamine requirement is of the greatest importance in testing vitamine B on pigeons.

7. There is slight evidence that with diminished food-intake beriberi symptoms are delayed on a diet free from vitamine B.

8. Alkali very markedly destroys vitamine B but has less action on vitamine D.

9. Autoclaving for three hours at 25 pounds pressure destroys vitamine B, but has less action on vitamine D.

10. Experiments on the effect of alkali and autoclaving were made, for the first time, on pigeons which were already in vitamine B equilibrium.

11. Contrary to existing opinions, growth of yeast or some other fungus takes D vitamine out of solutions but leaves B vitamine behind, as proved by experiments on pigeons and rats.

12. This method can be used for the elimination of vitamine D from a mixture of vitamine B and D. The yeast-cells retain the vitamine D very tenaciously after they have taken it out of solution. The experiments have to be continued to determine the optimum time and concentration necessary for the elimination of vitamine D from vitamine mixtures from various sources.

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CHART I. Composite curve of six pigeons, used for two hundred days, for testing some thirty fractions containing vitamin B, and others devoid of it.

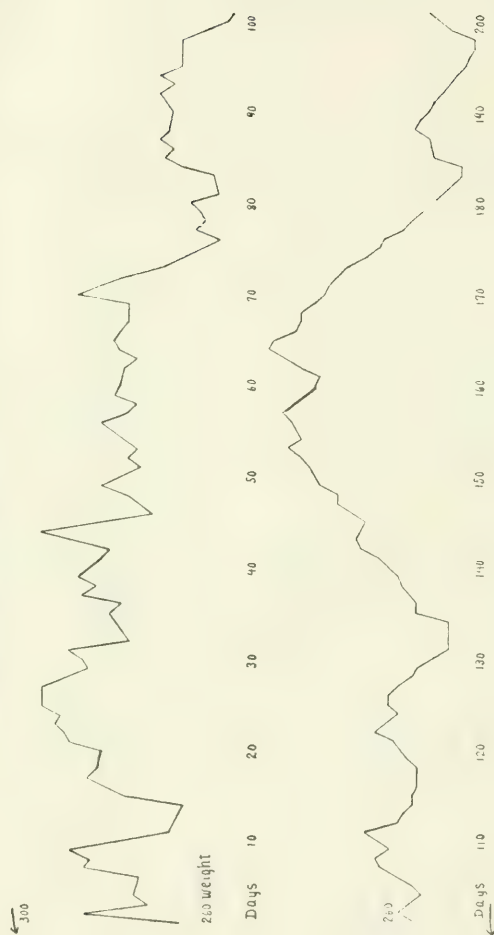
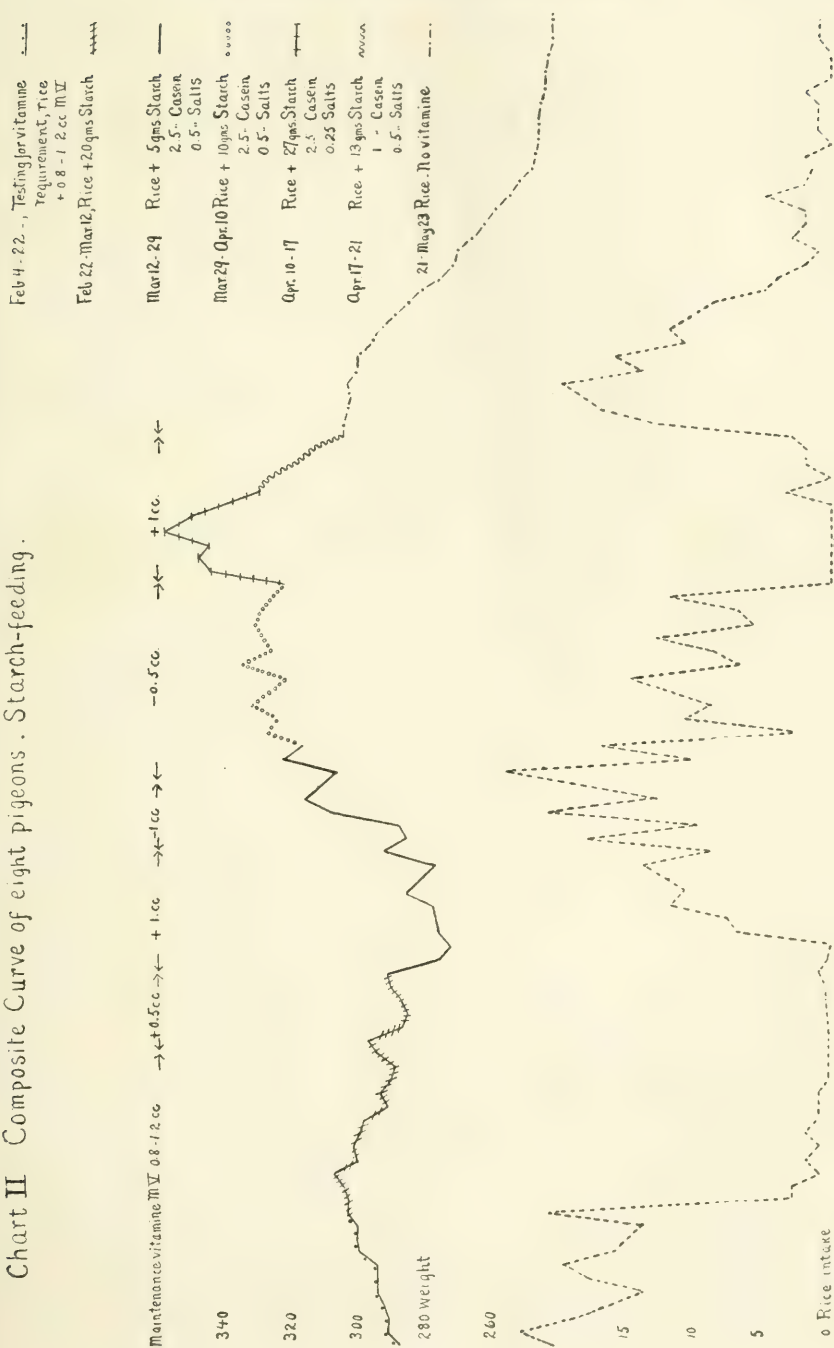


CHART II. Composite Curve of eight pigeons. Starch-feeding.

Chart II Composite Curve of eight pigeons. Starch-feeding.



12 17 22 27 4 9 14 19 24 29 0 5 10 15 20 25 30 35 40

CHART III.

Composite Curve of six pigeons on various amounts of vitamin B and on synthetic food.

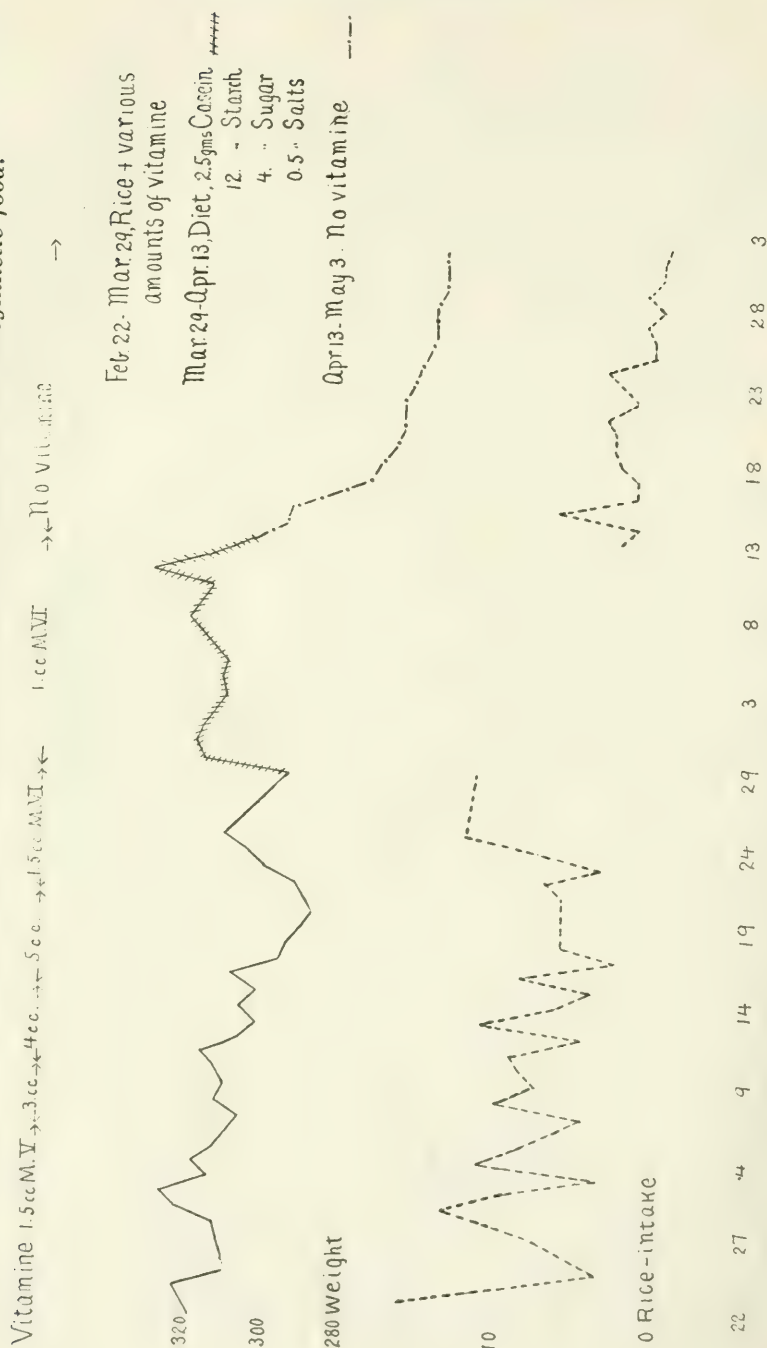


CHART IV.

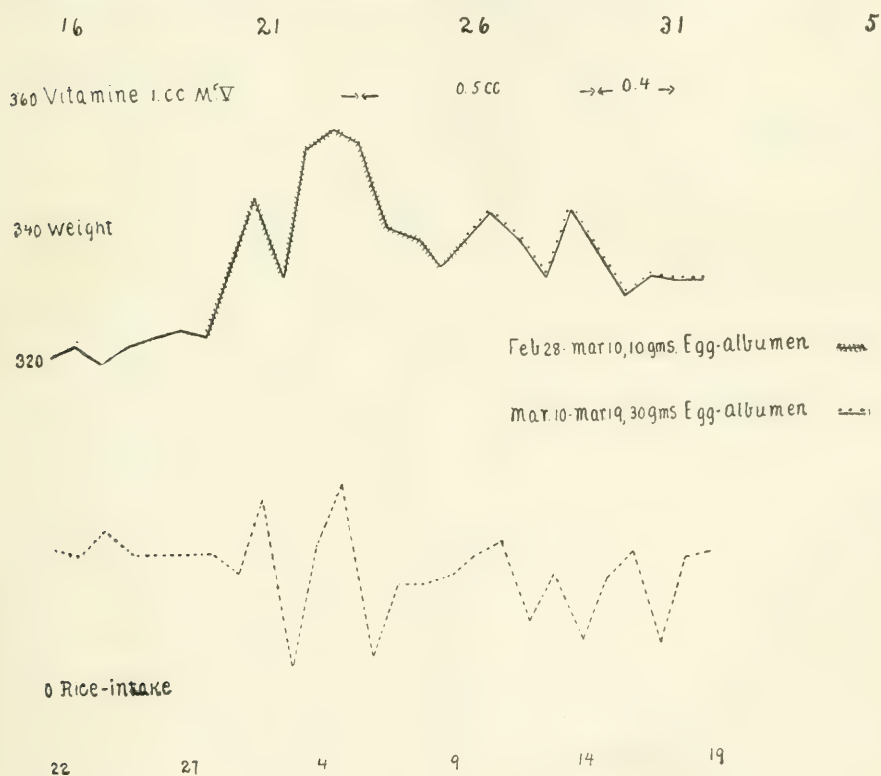
Composite curve of six pigeons on egg-albumen and low vitamine.

CHART V.

Composite curve of three pigeons on egg-albumen without vitamine.

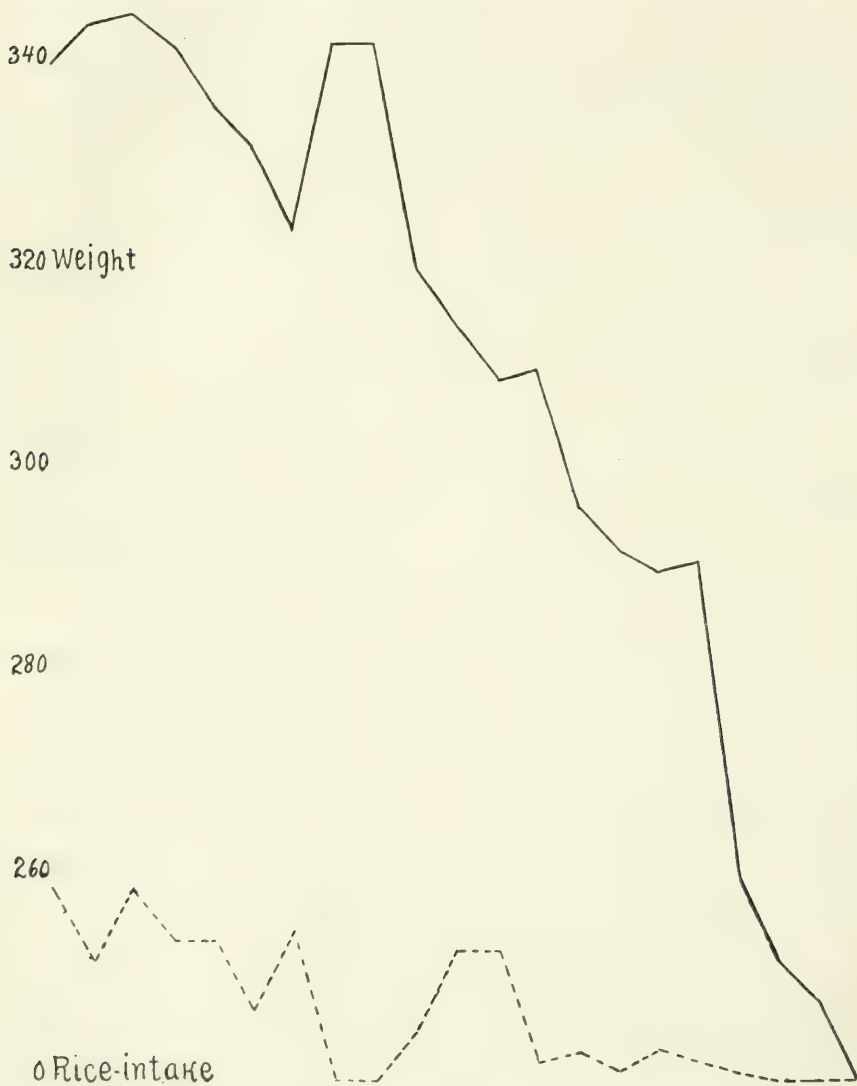


CHART VI.

*Comparison of pigeons on low vitamin and no vitamin.
Composite curves of two groups of six birds each.*

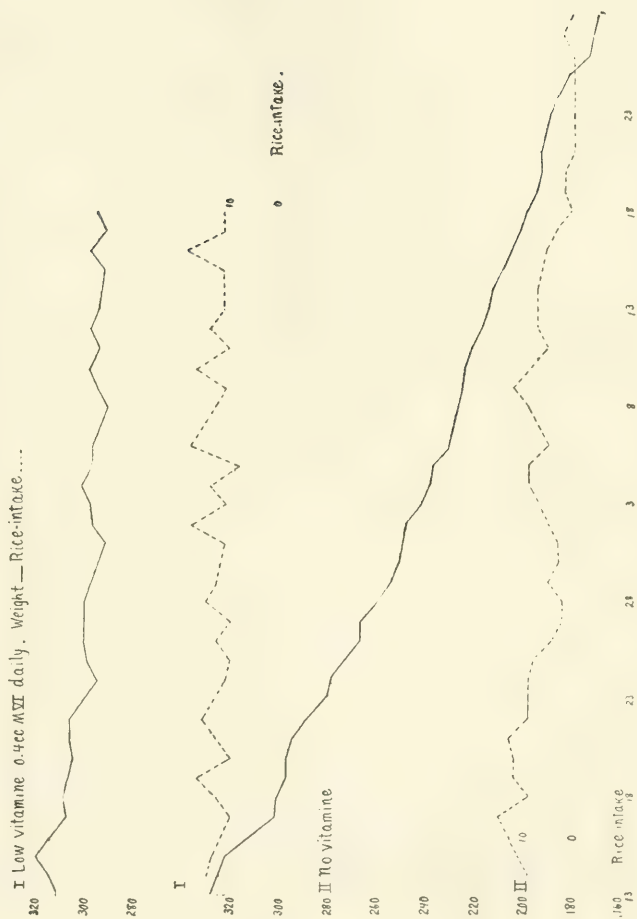


CHART VII.

Composite curves of average weight and rice-intake of fourteen pigeons.

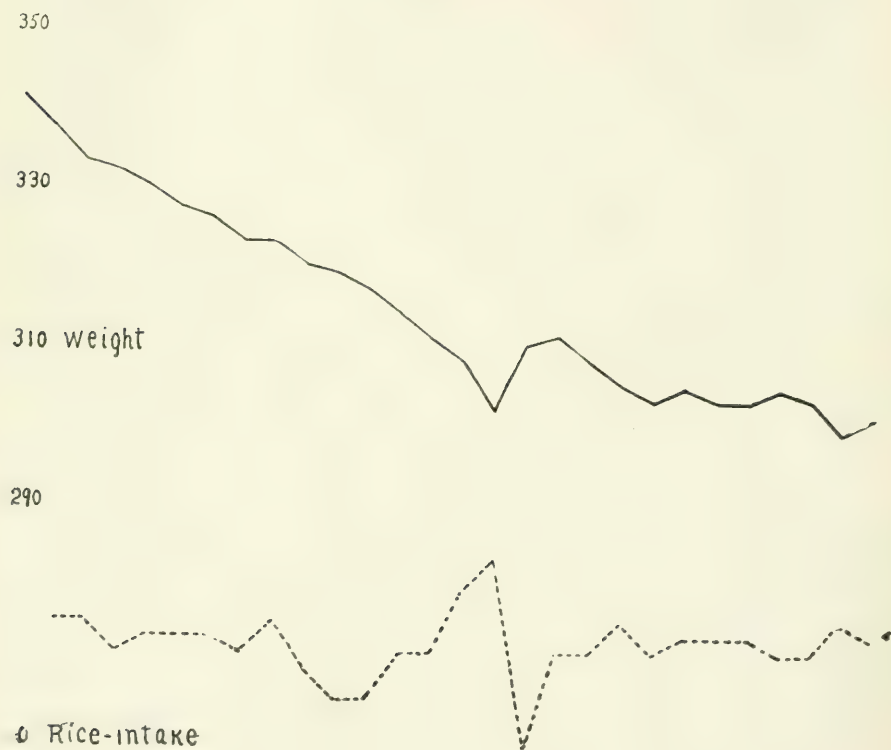


CHART VIII.

High vitamine requirement, 1.7-cc. Composite curve of six pigeons.



310 Average Rice-intake 12.2 gms. per day, $\frac{1}{28}$ of body weight.

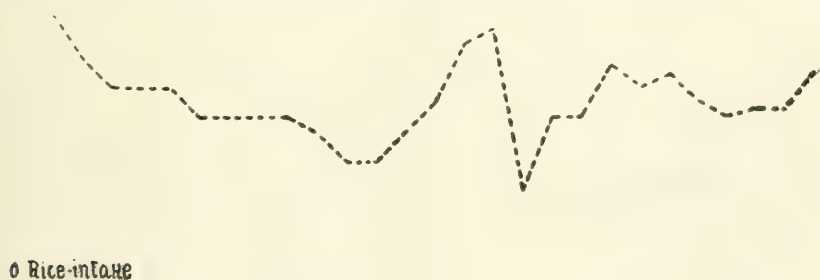


CHART IX.

Medium vitamine requirement, 1.3-1.5cc. Composite curve of four pigeons.



Average rice intake 11.5 gms. per day, $\frac{1}{20}$ of body weight.

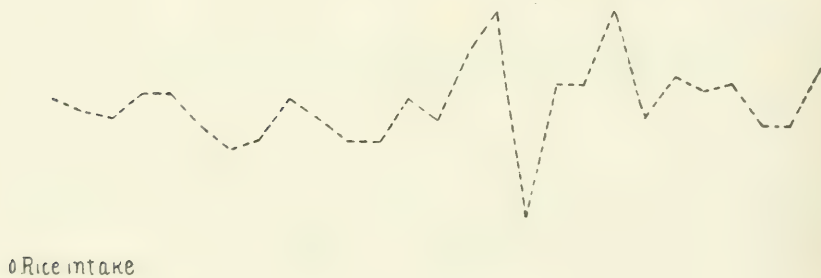


CHART X.

Low vitamine requirement, 0.9-1.2cc. Composite curve of four pigeons.



Average rice-intake 10.8 gms. per day, $\frac{1}{28}$ of body weight.

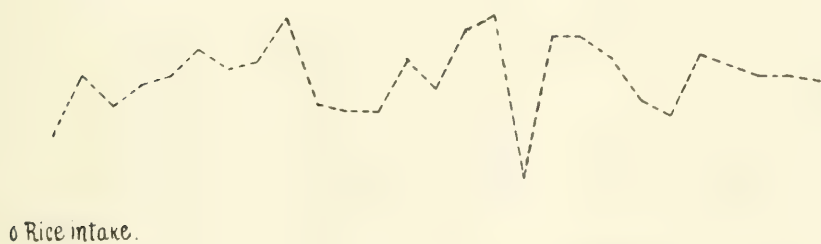


CHART XI.

Influence of microorganisms, action of alkali and autoclaving on a solution of vitamine B. Composite curves.

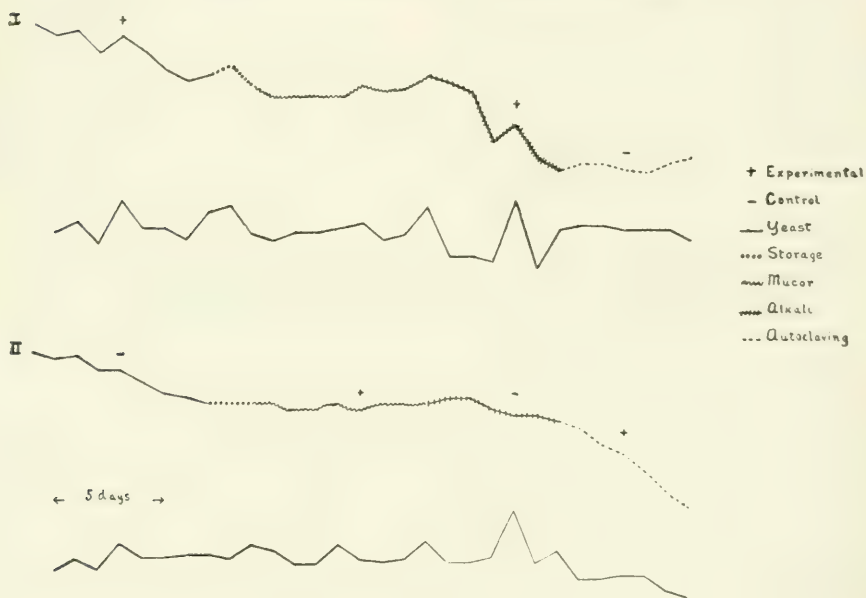


CHART XII.

solution of vitamine on the growth of young rats. Com- The effect of
sterilized and unsterilized yeast-inoculated posite curves of
nine rats. Sterilized---- *Unsterilized —*



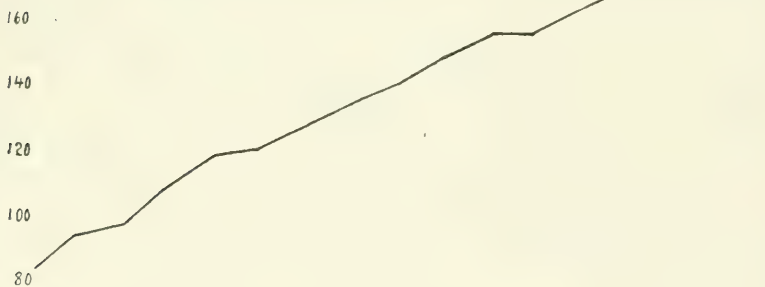
CHART XIII.

Comparison of pigeons and rats on vitamin B preparation.

A. Composite curve of six pigeons on M. VI vitamin B. 1.5-3 cc.



180 B Composite curve of five rats on Harris vitamin B. 2 cc



120 C. Composite curve of five rats on M. VI vitamin B. 2 cc

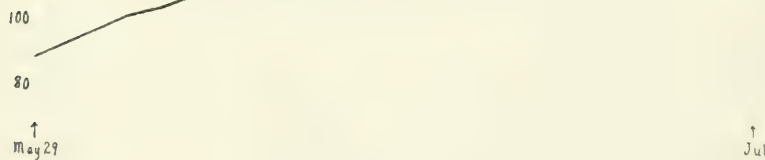


CHART XIV.
Composite curve of nine Pigeons.



INFLUENCE OF GLANDS WITH INTERNAL SECRETIONS ON THE RESPIRATORY EXCHANGE.

V. FURTHER OBSERVATIONS ON THE EFFECT OF SUPRARENAL INSUFFICIENCY (BY REMOVAL) IN THYROIDECTOMIZED RABBITS.

BY DAVID MARINE AND EMIL J. BAUMANN

From the Laboratory Division, Montefiore Hospital, New York City.

It has been shown by Golyakowski¹ on dogs, by Marine and Baumann² on rabbits, and by Scott³ on cats, that severe but sublethal crippling of the suprarenal function by vessel ligation, by freezing or by partial removal* with intact iodine containing thyroids usually leads to a prolonged increase in heat production. This increase in heat production usually begins within six days, and lasts from a week to several months falling gradually to or below the normal level. In a recent paper⁴ we presented six experiments on rabbits showing that when the thyroid gland was removed and the respiratory exchange allowed to fall to the myxedema level prior to crippling the function of the suprarenals, this increase in heat production either did not occur or was greatly lessened. These findings, we believed, showed that the thyroid gland by reason of its iodine containing hormone was necessary for the reaction of increased heat production following suprarenal injury. Further, these experiments suggested another thyroid—suprarenal interrelationship in addition to the chromophil tissue (epinephrin) — thyroid interrelation. The latter, since Asher

* As pointed out in previous papers, accessory cortical tissue is probably present in all rabbits and is readily demonstrated in about 70 per cent. of rabbits. On account of this fact, one can obtain a more complete gradation of partial suprarenalectomies by complete removal of the main glands, than by attempting to leave a portion of the main glands intact. The accuracy of this statement is strikingly illustrated in the series of rabbits reported in this paper. (See Table X). In cats this method is not applicable because accessory cortical tissue occurs too rarely. While, theoretically, it should be possible to obtain the desired sublethal suprarenal insufficiency in this animal (cat) by partial removal of the main glands, practically, its accomplishment would be an accident because (1) the amount of active tissue necessary for apparently normal life is very small and probably variable, and (2) the impossibility of preserving unimpaired the blood supply or of estimating the functional capacity of the unremoved fragment.

and Flack's work, is believed to be due in part to a direct stimulating effect of epinephrin on the thyroid gland through its sympathetic nervous mechanism. The nature of the former reaction is still unknown. As a working hypothesis we suggested that the suprarenal cortex, in addition to other functions, normally exercised a regulatory or inhibitory control over thyroid activity, and when this control was sufficiently crippled as a result of severe physical injury, the thyroid automatically responded with increased activity resulting in increased heat production, if sufficient thyroxin were discharged during this increased activity.

The purpose of this paper is to present in detail nine additional experiments on rabbits again showing that thyroidectomy prevents or greatly diminishes the rise in the respiratory exchange which usually follows severe bilateral but sublethal injury to the suprarenal glands with intact thyroids.

The protocols follow:

Protocol 1. Rabbit 283. Female — adult gray.

Sept. 9, 1921. Began metabolic studies.

Nov. 8. Under ether removed spleen.

Jan. 11, 1922. Under ether removed most of R and L thyroid lobes (slightly enlarged).

Mch. 7. Under ether removed R suprarenal gland (much enlarged).

Mch. 28. Under ether removed L suprarenal gland (markedly enlarged). Kidneys normal; very little abdominal fat.

Apr. 10. Has shown no evidence of suprarenal removal. Active, hearty and strong.

May 12. Normal in behavior. Being used for antibody work.

July 8. Under ether removed R and L ovaries (not notably enlarged, yellowish); no accessories seen.

July 14. Weight 2786 gm., has shown no symptoms since ovariectomy, wound healed, rabbit strong and hearty. Killed. Autopsy at once. A large, very vascular mass of thyroid at site of R ligature, 3 x 3 x 1 mm., no other thyroid found. Paras small; thymus atrophic, no visible lymphoid tissue and very little fat in area. Lungs normal, save for area emphysema along anterior border of left upper lobe. Heart small and normal in color; liver normal; spleen absent; pancreas hyperemic. R and L suprarenals absent, no accessories found in region. There is a large 3 mm. bright yellow (necrotic) accessory in R ovariectomy stump; also a 2 mm. vascular accessory suprarenal in L ovariectomy stump. Kidneys small and normal. Stomach distended with food, mucosa normal; very little abdominal or subcutaneous fat; mammary glands involuted.

TABLE I. *Rabbit 283.*

DATE	Room Temperature	Weight of Rabbit	O ₂ in grams, 2 hours	CO ₂ in grams, 2 hours	R. Q.	Total Calories, 2 hours	Calories per kgm. per hr.	Behavior of Animal	REMARKS
1921		GRAMS							
Sept. 13	25.2	2758	3.555	4.295	88	12.18	2.21	Quiet	
" 15	24.0	2740	3.670	4.380	87	12.53	2.29	"	
" 19	21.2	2788	3.735	4.420	86	12.76	2.29	"	
Nov. 6	21.2	2567	3.030	3.730	90	10.39	2.02	"	
" 10	22.0	2548	3.840	5.160	98	13.46	2.64	"	
" 12	22.0	2584	3.700	4.810	95	12.85	2.49	"	
" 16	22.8	2614	3.230	4.010	90	11.17	2.14	"	
" 18	25.0	2626	3.100	3.740	88	10.60	2.02	Mkd snuffles	
" 22	21.0	2632	3.400	4.170	89	11.72	2.23	Restless	
1922									
Jan. 5	22.0	2816	3.890	4.790	90	13.34	2.37	Quiet	
" 20	21.5	2836	3.840	5.290	100	13.59	2.40	"	
" 26	20.8	2786	4.370	4.680	78	14.59	2.62	"	
" 30	23.5	2883	4.410	5.240	86	15.12	2.62	Restless	
Feb. 3	21.2	2962	3.510	4.540	94	12.23	2.06	"	
" 6	22.5	3082	3.470	4.910	103	12.61	2.05	Quiet	Jan. 31 Thyroid-
" 11	21.6	3153	4.450	5.930	97	15.59	2.47	"	ectomy
" 16	18.0	3207	4.410	5.970	98	15.58	2.43	Restless	
" 23	24.0	3286	3.570	4.400	90	12.25	1.86	"	
Mch. 2	23.6	3317	3.760	4.720	91	13.03	1.96	Quiet	
" 6	21.4	3337	3.590	4.540	92	12.43	1.86	"	
" 9	23.2	3280	4.300	4.910	83	14.57	2.22	"	Mch. 7. R Supra- renalectomy Suprarenal much enlarged
" 13	23.4	3309	3.400	4.600	98	12.00	1.81	"	
" 21	20.6	3285	3.720	4.890	96	12.96	1.97	"	
" 23	23.8	3288	3.320	4.360	96	11.55	1.76	"	
" 27	23.5	3345	3.520	4.540	94	12.23	1.83	"	
" 30	23.0	3262	3.990	4.440	81	13.43	2.06	"	
Apr. 1	22.2	3216	3.730	4.470	87	12.78	1.99	"	
" 3	23.0	3187	3.560	4.660	95	12.45	1.95	"	
" 5	23.2	3217	3.930	4.900	91	13.53	2.10	"	
" 7	24.8	3216	3.880	4.580	86	13.22	2.06	"	
" 10	23.5	3223	3.310	3.980	87	11.38	1.77	"	
" 13	24.2	3202	3.880	4.580	86	13.22	2.06	"	
" 17	26.0	3253	3.930	4.440	82	13.30	2.04	"	
" 20	23.0	3159	3.760	4.490	87	12.84	2.03	"	
" 25	25.0	3210	3.870	4.440	83	13.17	2.05	"	
May 8	21.4	3162	3.670	4.580	91	12.65	2.00	"	

Protocol 2. Rabbit 284. Female — gray adult.

Sept. 13, 1921. Began metabolic studies.

Sept. 21. Under ether removed most of R and L thyroid lobes.

Oct. 1. Wound healed.

Oct. 27. Animal had been used for sheep cell antibody work.

Jan. 4, 1922. Under ether exposed thyroid area, searched for thyroid tissue, none found.

Jan. 10. Under ether removed R and L suprarenals completely. Abundant abdominal fat. No accessory suprarenal found.

Jan. 12. Somewhat dull, but eating ration.

Jan. 19. Wounds healed completely.

Jan. 21. Gave 25 mgm. KI by mouth.

Jan. 28. Hearty and strong.

Jan. 30. Gave 25 mgm. KI by mouth.

May 10. Being used for typhoid antibody work.

June 2. Nearly dead from intravenous injection of 1/4 cc. standard typhoid vaccine. Killed and autopsied at once. Thyroid lobes absent; there is a fragment of thyroid about 1 mm. in diameter at site of R stump ligature. Thymus atrophic, area replaced by fat; heart normal. Two small well encapsulated abscesses in lower right lobe of lung. Liver is small, flaccid and brownish yellow in color; distinct increase in lymphoid tissue in portal spaces. Kidneys very large brownish gray yellow, soft, high grade cloudy swelling. R and L suprarenals absent, sites clean. Ovaries are notably enlarged, bright yellow in color with many small graffian follicles. There is one large (0.5 cm. in length) and two small (1.0 mm. in diameter) accessory suprarenals near upper pole of R ovary and also two small (1 mm. in diameter) accessory suprarenals at upper pole of L ovary (all verified histologically). Abundant fat in all depositories. Spleen small; pancreas hyperemic; stomach mucosa normal. Rabbit had survived double suprarenalec-tomy indefinitely, probably due to abundant accessory cortical tissue.

TABLE II. *Rabbit 284.*

DATE	Room Temperature	Weight of Rabbit	O ₂ in grams, 2 hours	CO ₂ in grams, 2 hours	R. Q.	Total Calories, 2 hours	Calories per kgm. per hour	Behavior of Animal	REMARKS
1921									
Sept. 13	25.2	2760	3.550	4.455	91	12.30	2.23	Quiet	
" 15	24.0	2766	3.765	4.525	87	12.94	2.34	"	
" 19	21.2	2735	4.085	4.810	86	13.88	2.54	"	
" 27	22.0	2853	2.670	3.275	89	9.20	1.61	"	Sept. 21. Thyroid-ectomy
Oct. 3	24.3	2848	2.890	3.700	93	10.04	1.76	"	
" 7	24.4	2900	2.900	3.950	99	10.23	1.76	"	
" 24	24.0	2945	2.420	3.110	93	8.44	1.43	"	
Dec. 1	22.0	2880	2.420	3.380	102	8.68	1.51	"	
" 28	22.0	2880	2.420	3.380	102	8.68	1.51	"	
" 31	22.5	2927	2.980	3.670	90	10.22	1.75	"	
1922									
Jan. 3	20.0	2953	2.940	3.700	92	10.13	1.72	"	
" 6	21.5	2985	2.970	3.980	97	10.46	1.75	"	
" 12	21.5	2927	3.280	4.370	97	11.49	1.96	Dull	Jan. 4. Reoperated—no thyroid found Jan. 10. R and L Suprarenalectomy
" 14	21.5	2918	3.400	4.410	94	11.88	2.03	Quiet	
" 16	21.0	2872	3.260	4.300	96	11.40	1.98	"	
" 19	23.0	2922	3.080	4.140	98	10.80	1.85	"	
" 21	22.8	2905	3.130	4.060	94	10.93	1.88	"	
" 23	19.8	2840	3.450	4.020	85	11.70	2.06	"	
" 25	22.0	2851	2.950	3.910	96	10.36	1.82	"	
" 27	23.0	2846	3.190	3.990	91	11.02	1.94	Quiet	Jan. 21. KI-25 mgm.
" 30	22.0	2895	2.950	4.180	103	10.74	1.85	"	
Feb. 1	22.4	2895	2.860	3.930	100	10.10	1.74	"	
" 3	20.5	2916	3.320	4.330	95	11.57	1.98	"	
" 6	20.5	2977	3.130	4.390	102	11.28	1.89	"	
" 9	20.6	3006	2.850	4.020	103	10.33	1.72	"	
" 11	21.6	2987	3.140	4.150	96	11.00	1.84	"	
" 14	24.0	2929	2.910	4.130	103	10.61	1.81	"	
" 17	19.8	2940	3.280	4.150	92	11.36	1.93	"	
" 21	23.4	2953	2.910	3.860	96	10.23	1.73	"	
" 24	18.2	2951	3.060	4.120	98	10.75	1.82	"	
" 28	21.2	2944	3.280	4.230	94	11.39	1.93	"	
Mch. 3	20.5	2990	3.030	4.220	101	10.84	1.81	"	
" 7	22.5	3031	3.610	4.620	93	12.54	2.06	"	
" 17	17.8	2953	3.160	4.160	96	11.02	1.87	"	
" 21	20.6	2942	2.860	3.870	98	10.10	1.72	"	
" 28	24.0	2852	3.000	3.280	79	10.13	1.78	"	
Apr. 3	23.0	2770	2.870	3.160	80	9.65	1.74	"	
" 11	25.0	2777	3.050	3.230	77	10.17	1.83	"	
" 20	23.0	2765	2.780	3.770	99	9.76	1.77	"	
" 27	19.4	2814	3.200	4.190	95	11.19	1.99	"	

Protocol 3. Rabbit 287. Male — gray adult.

Sept. 13, 1921. Began metabolic studies.

Sept. 21. Under ether removed most of R and L thyroid lobes.

Dec. 27. Had been used for sheep cell antibody work.

Jan. 4, 1922. Under ether exposed thyroid area and searched for thyroid, none found.

Jan. 10. Under ether removed R and L suprarenals completely. Abundant abdominal fat. No accessory suprarenal seen.

Jan. 12. Active, eating.

Jan. 16. Respiration slow, fairly active, wounds healed.

Jan. 21. Gave 25 mgm. KI by mouth.

Jan. 28. Appears normal, active and hearty.

Jan. 30. Gave 25 mgm. KI by mouth.

Mch. 23. Head slightly rotated to left, chronic ear disease (external ears contain thick, reddish brown scales), active and hearty. Killed and autopsied at once. Well nourished, strong. A very vascular, actively hyperplastic mass of thyroid 3 mm. in diameter found on R side, none found on L. Thymus present, abundant lymphoid tissue accessory parathyroid in section; one small area of consolidation in each lower lobe of lungs. Heart appears normal; liver normal in gross appearance, microscopically, liver cells are very large with pale cytoplasm; spleen small; pancreas hyperemic. R and L suprarenals absent, sites clean; kidneys normal; stomach distended with food, mucosa normal; moderate fat in all depositories. Large hemorrhagic (3 mm. in diameter) accessory suprarenal in R spermatic cord, none found on L. Pituitary slightly enlarged. Pus in R middle ear, but brain and meninges appear normal.

TABLE III. *Rabbit 287.*

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DATE	Room Temperature	Weight of Rabbit grams	O ₂ in grams, 2 hours	CO ₂ in grams, 2 hours	R. Q.	2 hours Total Calories,	Calories per kgm. per hr.	Behavior of Animal	REMARKS
1921									
Sept. 13	23.6	2830	3.355	4.210	91	11.62	2.05	Quiet	
" 15	23.6	2731	3.685	4.330	85	12.61	2.31	"	
" 19	21.6	2701	4.045	4.445	80	13.58	2.51	"	
" 27	22.6	2808	3.305	3.940	87	11.27	2.01	"	Sept. 21. Thyroid-ectomy
Oct. 3	22.7	2781	2.980	3.770	92	10.32	1.86	"	
" 7	25.0	2828	3.345	4.245	92	11.62	2.05	"	
Dec. 28	22.0	2784	3.000	3.630	88	10.29	1.85	Rapid Resp.	
" 31	22.5	2840	3.440	4.460	94	12.01	2.11	Quiet	
1922									
Jan. 3	23.5	2815	3.640	4.180	84	12.29	2.18	"	Jan. 4. Reoperated
" 6	21.5	2839	3.840	4.700	89	13.21	2.33	"	—no thyroid found
" 12	20.0	2733	3.390	4.010	86	11.57	2.12	Dull	Jan. 10. R and L
" 14	21.5	2752	3.500	4.320	90	12.03	2.19	Quiet	Suprarenalectomy
" 16	21.0	2672	3.390	3.450	74	11.22	2.10	Dull	Resp. jerky and
" 19	23.0	2602	3.450	3.800	80	11.61	2.23	Quiet	rapid
" 21	22.8	2593	3.050	3.600	86	10.39	2.00	"	
" 23	19.8	2635	3.190	3.960	90	11.03	2.09	Quiet-dull	
" 25	22.0	2626	3.450	4.270	90	11.89	2.26	Quiet	
" 27	23.0	2585	3.170	3.840	88	10.89	2.11	Slight dyspnoea	
" 30	22.2	2585	3.200	4.190	95	11.19	2.16	Quiet	
Feb. 1	22.4	2629	2.920	3.930	98	10.25	1.95	"	Jan. 21. KI—25
" 3	20.5	2647	3.300	4.220	93	11.46	2.16	"	mgm.
" 6	20.5	2637	3.440	4.000	85	11.65	2.21	"	
" 9	20.6	2646	3.360	4.000	87	11.44	2.16	"	
" 11	21.6	2612	3.700	4.240	83	12.58	2.41	"	
" 14	24.0	2613	3.630	4.040	81	12.22	2.34	"	
" 17	19.8	2600	3.320	3.790	83	11.24	2.16	"	
" 21	23.4	2630	2.930	3.650	91	10.08	1.92	"	
" 24	18.2	2661	3.480	4.140	87	11.84	2.22	"	
" 28	21.2	2674	3.400	4.050	87	11.58	2.17	"	
Mch. 3	20.5	2650	3.510	3.810	79	11.76	2.22	"	
" 7	22.5	2663	3.030	3.820	92	10.46	1.96	"	
" 13	23.6	2634	2.810	3.280	85	9.55	1.81	"	
" 17	17.8	2659	3.110	3.770	88	10.69	2.01	"	
" 21	20.6	2617	3.210	3.680	83	10.92	2.09	Ataxic	

Protocol 4. Rabbit 288. Male — gray adult.

Sept. 4, 1921. Began metabolic studies.

Nov. 15. Under ether removed most of R and L thyroid lobes.

Jan. 10, 1922. Under ether removed R and L suprarenals completely. No accessory suprarenals seen; moderate abdominal fat; kidneys appear normal.

Jan. 12. Eating ration.

Jan. 17. Wounds healed. Active.

Jan. 21. Gave 25 mgm. KI by mouth.

Jan. 30. Gave 25 mgm. KI by mouth.

Mch. 17. Weight 1948 gm. Started glycerol extract of fresh ox suprarenal cortex, 5 cc. daily.

Mch. 30. Weight 2074 gm.

Apr. 15. Snuffles.

Apr. 24. Stopped suprarenal cortex.

Apr. 27. Not eating. Marked snuffles.

Apr. 28. Died. Weight 1880. gm. Autopsy while still warm. Two small, vascular thyroid masses about 1 mm. in diameter on R side, histologically both were actively hyperplastic; none on L. Thymus present, abundant lymphoid tissue; lungs normal; heart dilated and flabby. R and L suprarenals absent, sites clean; no accessory suprarenals found. Liver very dark red, small well marked increase in lymphoid tissue in portal spaces; pancreas hyperemic; spleen small; kidneys moderately pitted; testes smaller than normal; stomach contains considerable fluid, no food, mucosa intact. Aorta sclerotic at arch and at bifurcation.

DATE	Room Temperature	Weight of Rabbit	O ₂ in grams, 2 hours	CO ₂ in grams, 2 hours	R Q.	Total Calories, 2 hours	Calories per gram, per hour	Behavior of Animal	REMARKS
1921									
Sept. 20	23.5	grams 2140	3.905	4.670	87	13.36	3.12	Restless	
" 28	24.7	2141	3.685	4.585	90	12.77	2.98	"	
Nov. 4	22.0	2216	2.890	3.260	82	9.34	2.11	Quiet	
" 11	23.0	2172	2.850	3.110	79	9.60	2.21	"	Nov. 15. Thyroid-ectomy
" 22	21.0	2344	2.790	3.570	93	9.69	2.07	"	
" 30	22.0	2451	3.090	3.750	88	10.63	2.17	"	
Dec. 7	22.0	2511	2.950	4.030	99	10.43	2.08	"	
1922									
Jan. 5	22.0	2584	2.960	3.880	95	10.36	2.01	"	
" 9	22.0	2557	3.020	3.920	94	10.56	2.06	"	Snuffles
" 12	20.0	2420	2.870	3.290	83	9.76	2.02	"	Jan. 10. R and L Suprarenalectomy
" 14	21.5	2405	2.880	3.550	90	9.89	2.06	"	
" 16	21.0	2393	2.950	3.740	92	10.24	2.14	"	
" 19	23.0	2336	2.860	3.470	88	9.84	2.11	"	
" 21	22.8	2316	2.820	3.360	87	9.61	2.07	"	
" 23	19.8	2394	3.000	3.590	87	10.27	2.14	"	Jan. 21. KI—25 mgm.
" 25	22.0	2435	3.070	4.030	95	10.76	2.21	"	
" 27	23.0	2334	2.530	3.530	101	9.07	1.94	"	
" 30	22.0	2298	2.810	3.580	93	9.72	2.11	"	
Feb. 1	22.4	2243	2.380	3.160	97	8.31	1.85	"	Jan. 30. KI—25 mgm.
" 3	20.5	2210	2.490	2.950	86	8.51	1.93	"	
" 6	20.5	2278	2.930	3.700	92	10.13	2.22	"	
" 9	20.6	2302	3.070	4.050	96	10.73	2.33	"	
" 11	21.6	2286	2.970	3.860	95	10.31	2.26	"	
" 14	24.0	2235	2.760	3.500	92	9.58	2.14	"	
" 17	19.8	2169	3.000	3.480	84	10.23	2.36	"	
" 21	23.4	2160	2.200	3.190	105	8.20	1.90	"	
" 24	18.2	2168	2.720	3.390	91	9.36	2.16	"	
" 28	21.2	2112	2.890	3.360	85	9.78	2.32	"	
Mch. 3	20.5	2105	2.500	3.040	88	8.62	2.05	"	
" 7	22.5	2043	2.330	2.770	86	7.99	1.96	"	
" 13	23.4	2017	2.830	2.950	82	8.84	2.19	"	
" 17	17.8	1992	2.270	3.000	96	7.95	2.00	Quiet-dull	Mch. 17. Adr. cortex emulsion (5cc. daily)
" 20	20.6	1978	2.820	3.340	86	9.64	2.44	Quiet	
" 28	24.0	2077	2.890	3.490	86	11.54	2.38	"	
Apr. 3	23.0	2062	2.750	3.270	86	9.44	2.29	"	
" 7	24.8	2059	2.880	3.260	82	9.77	2.37	"	
" 11	25.0	1998	2.750	3.000	79	9.26	2.32	"	
" 17	25.5	2048	2.750	3.050	81	9.23	2.25	"	
" 20	23.0	2057	2.940	3.260	81	9.86	2.40	"	
" 24	24.0	2115	3.050	3.380	81	10.22	2.42	"	

Protocol 5. Rabbit 291. Male — adult, black.

Sept. 21, 1921. Began metabolic studies; used for antibody work.

Jan. 18, 1922. Under ether removed spleen.

Feb. 2. Under ether removed most of R and L thyroid lobes.

Mch. 7. Under ether removed R suprarenal.

Mch. 28. Under ether removed L suprarenal; moderate abdominal fat, slight pitting of kidney cortex.

Apr. 1. Active, eating well.

Apr. 9. Soft stools, dull, not eating well.

Apr. 14. Soft stools, losing weight, eats carrot, but very little oats.

Apr. 18. Weaker, eats very little carrot. Snuffles.

Apr. 22. Died this morning, autopsy at once. R and L thyroid lobes absent, no accessories found. On microscopic examination of thyroid area a few hyperplastic follicles found attached to thyroid cartilage. Thymus atrophic; lungs normal; heart small and contracted; liver small, flaccid, very dark brown; spleen absent, no accessories found. R and L suprarenals absent. One small 1 mm. hemorrhagic accessory found in L spermatic cord, no others found after careful search. Kidneys show slight pitting of cortex. Moderate abdominal fat. Testes normal; stomach contains moderate amount of food and fluid, mucosa intact. Hypophysis not notably enlarged. Microscopic examination — slight lymphoid infiltration in portal spaces of liver and in kidney.

TABLE V.
Rabbit 291.

DATE	Room Temperature	Weight of Rabbit	O ₂ in grams, 2 hours	CO ₂ in grams, 2 hours	R. Q.	Total Calories, 2 hours	Calories per kgm. per hour	Behavior of Animal	REMARKS
1921		grams							
Sept. 21	23.5	2212	4.065	4.695	84	14.55	3.29	Restless	Jan. 18. Splenectomy.
" 28	24.2	2272	4.165	5.185	91	14.32	3.15	"	
Nov. 5	20.5	2497	3.350	4.720	102	12.13	2.43	Quiet	Feb. 2. Thyroidectomy
" 11	23.0	2402	3.300	3.730	82	11.18	2.33	"	
Dec. 7	22.4	2515	3.610	4.490	90	12.50	2.49	"	
1922									
Jan. 5	22.0	2537	3.620	4.540	91	12.53	2.47	"	Mch. 7. R Supra-renalectomy
" 20	21.5	2380	3.870	4.670	88	13.24	2.78	"	
" 23	19.8	2475	3.930	5.160	95	13.78	2.78	Restless	Mch. 28. L Supra-renalectomy
" 25	22.0	2459	3.610	4.620	93	12.54	2.55	Quiet	
" 27	23.6	2441	3.380	4.020	86	11.60	2.38	"	
" 30	23.5	2508	3.710	4.660	91	12.87	2.57	"	
Feb. 1	23.0	2515	3.840	4.960	94	13.36	2.66	"	
" 9	22.0	2637	3.170	4.260	98	11.11	2.11	"	
" 16	19.0	2611	2.930	4.040	100	10.38	1.99	"	
" 23	24.0	2736	3.060	3.970	94	10.69	1.95	"	
" 28	21.4	2730	2.540	3.880	111	9.97	1.83	"	
Mch. 7	22.5	2790	2.940	3.930	97	10.33	1.85	"	
" 10	23.2	2753	2.280	3.550	113	9.12	1.66	"	
" 13	23.4	2747	2.930	3.820	95	10.20	1.86	"	
" 20	23.2	2799	2.620	3.710	103	9.53	1.70	"	
" 27	23.0	2850	2.700	3.830	103	9.84	1.73	"	
" 30	23.0	2770	2.790	3.270	85	9.52	1.72	"	
Apr. 1	21.8	2764	3.210	3.990	90	11.11	2.01	"	
" 3	23.0	2774	2.900	3.770	95	10.07	1.82	"	
" 5	23.2	2732	2.600	3.310	93	8.99	1.64	"	
" 7	22.5	2692	3.030	3.540	85	10.31	1.91	"	
" 10	23.5	2740	2.530	3.100	89	8.71	1.59	Diarrhea: urinous odor Mkd. asthenia	
" 13	23.8	2620	2.220	2.800	92	7.67	1.46	Moribund	
" 17	24.2	2692	2.170	2.450	82	7.34	1.36		
" 20	23.0	2459	1.840	2.160	85	6.29	1.28		

Protocol 6. Rabbit 306. Female — black and white. (Born in Laboratory, July 1, 1921.)

Dec. 2, 1921. Began metabolic studies.

Jan. 18, 1922. Under ether removed spleen.

Feb. 2. Under ether removed most of R and L thyroid lobes.

Mch. 7. Under ether removed R suprarenal.

Mch. 28. Under ether removed L suprarenal.

Apr. 1. Slight purulent discharge from nose.

Apr. 10. Chronic bilateral external ear disease.

Apr. 29. Eating well, but dull.

May 31. Under ether froze R and L ovaries with ethyl chloride. Ovaries notably enlarged and bright yellow in color.

June 5. Has shown no effects of freezing ovaries, active and strong, in excellent condition. Killed. Both ears contain large masses of thick, dry, brownish scales, putrefactive odor. Skin of body is dry and scaly and fur thin. No thyroid found on careful search, area saved for microscopic examination. Thymus atrophic, area replaced by fat. Each lung shows a very small area of consolidation along anterior margin of upper lobes. Heart normal; liver seems very small, otherwise normal; spleen absent, no accessories found; pancreas not hyperemic. R and L suprarenals absent, sites clean. In the capsule of L kidney near upper pole is a large accessory suprarenal 2 x 3 mm. with large veins emerging and draining into L lumbo-suprarenal vein. Two small (1 mm. in diameter) accessories at upper pole of R ovary, each with a separate large vein draining into L ovarian vein. Kidneys smooth, normal; abundant abdominal fat. Pituitary perhaps slightly enlarged.

TABLE VI. *Rabbit 306.*

DATE	Room Temperature	Weight of Rabbit	O ₂ in grams, 2 hours	CO ₂ in grams, 2 hours	R. Q.	Total Calories, 2 hours	Calories per kgm. per hour	Behavior of Animal	REMARKS
1921		grams							
Dec. 2	24.5	1833	2.860	3.150	80	9.62	2.63	Quiet	
" 7	21.8	1847	2.770	3.310	87	9.47	2.56	"	
1922									
Jan. 5	21.8	1949	3.390	3.430	74	11.15	2.86	Restless	Ears scalded, sloughing
" 12	21.0	1992	3.220	4.220	95	11.27	2.83	"	Ears healed
" 17	24.0	1954	3.060	3.510	83	10.41	2.66	"	
" 20	21.5	1916	3.150	3.940	91	10.88	2.84	Quiet	Jan. 18. Splenectomy
" 23	20.2	2000	3.420	4.360	93	11.84	2.96	"	Moisture
" 25	22.0	1954	3.350	3.880	84	11.40	2.92	"	"
" 27	23.6	1938	3.110	3.690	86	10.65	2.75	"	
" 30	25.5	1880	3.140	3.560	82	10.67	2.84	"	
Feb. 1	22.4	1886	2.910	3.510	88	9.95	2.65	"	
" 10	26.6	2008	2.480	3.030	89	8.51	2.12	"	Feb. 2. Thyroidectomy
" 21	24.6	2157	2.540	3.160	90	8.80	2.04	"	
" 27	22.8	2223	2.520	3.300	95	8.81	1.98	"	
Mch. 6	21.4	2204	2.650	3.460	95	9.24	2.10	"	
" 9	22.8	2278	2.550	3.450	98	9.00	1.98	"	Mch. 7. R Supra-renalectomy
" 11	20.2	2303	2.620	3.450	96	9.14	2.08	"	
" 14	22.2	2264	2.520	3.400	98	8.87	1.96	"	
" 17	19.8	2207	2.960	3.630	89	10.20	2.31	"	
" 20	23.2	2211	2.420	3.160	95	8.44	1.91	"	
" 23	23.2	2170	2.960	3.460	85	10.07	2.32	"	
" 27	23.0	2285	2.150	3.150	107	8.09	1.77	"	
" 30	21.8	2201	2.850	3.320	85	9.67	2.20	"	Mch. 28. L Supra-renalectomy
Apr. 1	23.0	2231	2.720	3.320	89	9.33	2.09	"	
" 3	23.0	2238	2.770	3.620	95	9.67	2.16	"	
" 5	23.2	2257	3.040	3.680	88	10.43	2.31	"	
" 7	24.8	2264	2.640	3.560	98	9.29	2.05	"	
" 10	22.5	2290	2.360	3.240	100	8.32	1.82	"	Bilateral ear infection
" 13	23.8	2238	2.480	3.280	96	8.69	1.94	"	
" 17	25.5	2278	2.680	3.270	89	9.19	2.02	"	
" 20	22.5	2160	2.410	3.280	99	8.49	1.97	"	External and middle ear infection
" 25	25.0	2207	2.770	3.250	85	9.46	2.14	"	Odor of putrefaction
May 8	21.6	2206	2.710	3.280	87	9.32	2.11	"	

Protocol 7. Rabbit 323. Male — white adult.

Jan. 18, 1922. Began metabolic studies.

Feb. 2. Under ether removed most of R and L thyroid lobes, enlarged and hyperemic.

Feb. 28. Under ether removed R suprarenal. Rabbit has always been dull and inactive.

Apr. 11. Under ether removed L suprarenal; kidneys normal; abundant fat.

Apr. 14. Eating well, as active as usual.

Apr. 20. Wounds healed, stiches removed.

July. 7. Has been used in antibody studies. Apparently normal. Killed. Weight 2233 gm. One large thyroid fragment 3 x 2 mm. on R side at site of ligature. None found on L. External paras normal; thymus atrophic; heart and lungs normal; liver normal; kidneys normal. R and L suprarenals absent, sites clean, no accessory suprarenals found in region of suprarenals nor along path of descent of testes. Testes examined carefully for accessories. Two and probably three small ones found. Testes smaller than usual. Spleen small; pancreas hyperemic; abundant abdominal fat; lymph glands not enlarged.

TABLE VII. *Rabbit 323*

DATE	Room Temperature	Weight of Rabbit	O ₂ in grams, 2 hours	CO ₂ in grams, 2 hours	R Q.	Total Calories, 2 hours	Calories per kgm. per hour	Behavior of Animal	REMARKS
1922		grams							
Jan. 26	21.6	2354	3.320	4.480	98	11.69	2.48	Quiet	Two runs for training
" 28	22.0	2374	3.370	4.480	97	11.78	2.48	"	
Feb. 1	24.0	2455	3.520	4.240	88	12.02	2.45	"	
" 10	23.0	2365	2.950	4.160	103	10.69	2.26	"	Feb. 2. Thyroid-ectomy
" 17	20.0	2357	2.670	3.250	89	9.13	1.94	"	
" 24	20.6	2442	2.600	3.480	97	9.15	1.87	"	
Mch. 3	22.0	2459	2.400	3.240	98	8.45	1.72	"	Cyanotic
" 17	19.6	2493	2.770	3.550	93	9.64	1.93	"	
" 23	21.8	2506	2.890	3.590	90	10.00	1.99	"	
" 27	23.5	2585	2.710	3.600	97	9.46	1.83	"	
" 30	22.0	2446	3.010	3.710	90	10.33	2.11	"	Mch. 28. R Supra-renalectomy
Apr. 6	22.5	2447	2.870	3.690	94	9.94	2.03	"	
" 13	23.2	2522	2.860	3.670	93	9.96	1.98	Dull	
" 15	23.2	2550	2.830	3.880	100	9.97	1.95	"	Apr. 11. L Supra-renalectomy
" 17	26.0	2470	2.810	3.420	89	9.61	1.95	"	Marked asthenia
" 20	22.5	2448	2.760	3.700	97	9.73	1.99	"	
" 22	23.8	2322	2.630	3.420	95	9.13	1.97	"	Unable to hold head up
" 24	21.8	2453	3.090	3.810	90	10.61	2.16	Quiet	Ear disease
" 27	17.6	2370	3.070	4.080	97	10.73	2.26	"	
May 1	25.2	2380	2.730	2.930	78	9.13	1.92	Very dull	Severe ear disease
" 8	21.4	2347	2.880	3.330	84	9.79	2.08	"	No asthenia
" 16	21.2	2360	3.040	3.800	91	10.49	2.22	Dull	

Protocol 8. Rabbit 325. Female — gray adult.

Jan. 25, 1922. Began metabolic studies.

Mch. 7. Under ether removed most of R and L thyroid lobes, vascular, slightly enlarged.

Apr. 5. Under ether removed R suprarenal, enlarged.

Apr. 11. Under ether removed L suprarenal and one small accessory on peritoneum slightly external to gland.

Apr. 14. In good condition, eats well.

Apr. 18. No evidence of suprarenal injury has developed, active, hearty and strong.

July 10. Was bred several times since Apr. 18, but never became pregnant. Killed, autopsy at once. There is a fragment of very hyperemic thyroid 3 x 1 mm. on L side and on R side there are two small fragments (1) 2 x 1 mm. and (2) 1 x 1 mm. The two external parathyroids are normal in size and appearance. Thymus atrophic, area replaced by fat; lungs and heart normal; liver is very large, surface lobulated, many minute white fibromata in capsule. The lower liver is unusually large, about twice the weight of the upper. R suprarenal absent. At site of L suprarenal there is a thin mass 2 x 2 mm. of bright yellow tissue surrounding old ligature. Microscopic examination shows only pigmented fat. At upper pole of R ovary there is a very vascular large accessory adrenal 5 x 2.5 mm. Ovaries are very large, two or three times normal size, bright yellow in color with many small graafian follicles. Kidneys are normal; spleen small; pancreas not hyperemic; stomach distended with food, mucosa intact.

TABLE VIII. *Rabbit 325.*

DATE	Room Temperature	Weight of Rabbit	O ₂ in grams, 2 hours	CO ₂ in grams, 2 hours	R Q.	Total Calories, 2 hours	Calories per kgm. per hour	Behavior of Animal	REMARKS
1922									
Jan. 28	22.2	2333	3.180	4.340	99	11.24	2.41	Quiet	Two runs for training
Feb. 2	23.2	2395	3.570	4.340	88	12.30	2.56	Rapid Resp.	
" 4	20.6	2389	3.460	4.240	89	11.91	2.49	Quiet	
" 7	20.5	2391	3.420	4.030	86	11.63	2.43	"	
" 10	24.0	2403	3.410	4.340	93	11.78	2.45	"	Mch. 7. Thyroid-ectomy
" 21	24.4	2442	3.420	4.210	90	11.72	2.40	"	
Mch. 4	22.0	2603	3.920	4.970	92	13.61	2.61	"	
" 14	21.2	2720	3.090	4.080	96	10.81	1.99	"	
" 21	21.0	2698	3.040	3.970	95	10.60	1.97	"	Apr. 5. R Supra-renalectomy Apr. 11. L Supra-renalectomy Recently pregnant
" 28	20.5	2770	2.770	3.890	102	9.99	1.80	"	
Apr. 13	23.2	2790	2.930	3.840	95	10.26	1.87	"	
" 15	23.5	2791	2.880	4.000	101	10.27	1.84	"	
" 17	26.0	2746	3.660	3.980	79	12.28	2.24	"	
" 20	22.5	2714	3.570	4.020	82	12.04	2.22	"	
" 22	23.8	2672	3.140	4.030	93	10.94	2.05	"	
" 24	21.8	2715	3.760	4.560	88	12.93	2.38	"	
" 27	17.6	2672	3.440	4.260	90	11.86	2.22	"	
May 1	25.2	2728	3.280	3.810	85	11.09	2.03	"	
" 8	21.0	2696	3.310	3.940	87	11.27	2.09	"	
" 13	23.2	2882	3.120	3.860	90	10.75	2.00	"	
" 16	21.2	2712	3.290	4.320	95	11.54	2.13	"	

Protocol 9. Rabbit 326. Fawn colored female.

Jan. 25, 1922. Began metabolic studies.

Mch. 7. Under ether removed most of R and L thyroid lobes, enlarged and hyperemic.

Apr. 5. Under ether removed R suprarenal.

Apr. 11. Under ether removed L suprarenal.

Apr. 14. Active, hearty; has shown no dullness since operation.

Apr. 18. In heat, bred.

May 19. Gave birth to 6 young.

July 8. Reared and weaned young. Under ether removed R and L ovaries, distinctly enlarged and bright yellow. Examination of ovarian region for accessory suprarenals unsatisfactory.

July 12. Weight 2249 gm. In excellent condition, no reaction from gonadectomy. Killed. Breasts involuting rapidly. Two accessory (?) thyroids in midline, one on fascia at notch on upper border of thyroid cartilage about 1 mm. in diameter and another a few mm. above, about 0.5 mm. in diameter. (It is possible these may be auto transplants from fragments dropped at time of removal). There is another thin veil of thyroid tissue on anterior surface of trachea in region of old isthmus. No thyroid found on L side. On R side there are two separate fragments each about 1 mm. in size, hyperemic. External parathyroids normal; thymus atrophic, no fat in area; lungs and heart normal; liver normal; spleen slightly enlarged; pancreas hyperemic. R and L suprarenals absent. Large accessory suprarenal 3 x 1.5 mm. on lateral abdominal wall, external and above kidney. A large, long vein extends directly into the renal vein. No definite suprarenal tissue in region of ovaries. R and L ovaries absent. Sites examined histologically. On R side below renal artery is a grayish yellow mass 4 x 1 mm. possibly suprarenal or lymph gland. Kidneys normal; stomach distended with food, mucosa normal. Very little fat visible anywhere.

TABLE IX. *Rabbit 326*

DATE	Room Temperature	Weight of Rabbit grams	O ₂ in grams, 2 hours	CO ₂ in grams, 2 hours	R Q.	Total Calories, 2 hours	Calories per krm. per hour	Behavior of Animal	REMARKS
1922									
Jan. 28	22.2	2549	3.580	4.410	90	12.28	2.41	Quiet	Two runs for training
Feb. 2	23.8	2650	3.860	4.880	92	13.36	2.52	"	
" 4	20.6	2702	3.760	4.600	89	12.93	2.39	"	
" 7	20.5	2708	4.240	5.070	87	14.50	2.68	"	
" 21	24.4	2600	3.480	4.360	91	12.04	2.31	"	
Mch. 14	21.2	2902	3.150	4.460	103	11.46	1.97	"	Mch. 7. Thyroid-ectomy
" 21	21.0	2922	3.390	4.460	95	11.78	2.02	"	
" 27	23.5	2997	2.910	4.140	101	10.40	1.74	"	
" 28	24.0	2983	3.700	4.040	79	12.47	2.09	"	Apr. 5. R Supra-renalectomy
Apr 13	23.2	3002	3.610	4.850	98	12.65	2.11	"	Apr. 11. L Supra-renalectomy
" 15	23.5	2989	3.170	4.390	101	11.28	1.89	"	Bred Apr. 18
" 20	26.0	2916	2.990	3.750	91	10.35	1.78	"	
" 20	22.5	2932	3.590	4.710	95	12.58	2.10	"	
" 22	23.8	2921	3.160	4.000	92	10.95	1.87	"	
" 24	21.8	2972	3.280	4.526	100	11.61	1.95	"	
" 27	17.6	3022	3.760	5.020	97	13.20	2.18	"	
May 1	25.2	3170	3.660	4.210	84	12.37	1.95	"	
" 8	21.0	3281	4.140	5.270	93	14.31	2.18	"	
" 13	23.2	3310	4.200	4.950	86	14.29	2.16	"	
" 16	21.2	3383	4.680	5.570	87	15.93	2.35	"	Near term—placed in large cage.
" 18	20.8	3366	5.100	5.570	79	17.19	2.60	"	May 20. Gave birth to young
" 26	25.0	2922	3.640	4.770	95	12.74	2.18	"	Nursing young
June 17	23.0	2427	3.640	4.940	99	11.79	2.43	Quiet	
" 26	23.6	2287	4.030	3.240	90	11.22	2.45	"	
" 28	25.2	2272	3.400	2.970	83	10.09	2.22	"	

The more important general data of the nine experiments here reported and also of the six experiments previously reported are summarized in Table X.

TABLE X.

Sex	Rabbit No.	Interval before Thyroidectomy	Interval between Thyroidectomy and removal of 2nd Suprarenal	Duration of life after double Suprarenalectomy	Average normal metabolism Calories per kg. per hr.	Average metabolism after Thyroidectomy Calories per kg. per hr.	Percentile decrease after Thyroidectomy	Average metabolism during first two weeks following Suprarenalectomy Calories per kg. per hr.	Percentile increase or decrease after Suprarenalectomy	Fragments or Accessory Thyroids at Autopsy	Accessory Suprarenals at Autopsy *	REMARKS
		da.	da.	da.								
m	271	14	23	20	2.25	1.86	17	1.62	-13	none found	none found	
m	267	14	23	Died 35	2.33	1.92	18	1.68	-12	none found	none found	
m	270	14	23	Died 26	2.41	2.04	15	1.87	- 8	1-2 mm. fragment	none found	
m	272	14	23	Died. 63	2.62	1.95	26	1.82	- 7	2 fragments 1x2 mm.	7 large	
m	291	134	54	Killed 25	2.54	1.84	28	1.75	- 5	few follicles microscopical trace	1-1 mm.	Splenectomy
f	266	14	23	Died 14	2.67	1.83	31	1.83	0	microscopical	none found	
m	288	73	56	Died 118	2.43	2.08	14	2.09	0	2-1 mm. fragments	none found	KI
f	306	62	54	Died. 69	2.62	2.05	22	2.08	0	none found	2-1 mm. 1-3x2 mm.	Splenectomy KI
f	326	38	35	Killed. 94	2.50	1.95	22	1.98	0	2 accessories 3 fragments 1 mm.	1-3x1.5 mm. 1-0.5 mm. possibly others	
m	323	7	54	Killed. 87	2.47	1.93	22	2.00	+ 4	1-3x2 mm. fragment	3-1 mm.	
m	287	8	111	Killed. 72	2.29	2.01	10	2.12	+ 5	1-3 mm. fragment	1-3 mm.	KI
m	269	14	23	Killed. 63	2.25	1.77	21	1.87	+ 6	1-2 mm. fragment	7	
f	283	140	56	Killed. 109	2.28	1.89	17	2.00	+ 6	1-3x3 fragment	2 large	Splenectomy
f	325	41	35	Killed. 91	2.48	1.92	23	2.12	+10	1-3x1 2-2x1 fragments	1-5x3 mm. 1-2 mm.	
f	284	8	111	Killed. 143	2.37	1.72	27	1.94	+13	1-1 mm. fragment	5 1 very large	KI

* Complete surgical removal of both main glands had been made in all cases as shown by careful gross and microscopic autopsy checks.

Very carefully search was made for fragments of or accessory suprarenal tissue and also for thyroid tissue at autopsy. All definite or suggestive masses were checked by histological examination. In every case both main suprarenal glands were found to have been completely removed. In ten of the fifteen cases accessory suprarenal cortical tissue was demonstrated. As many as seven separate accessory masses have been found in a single animal. These masses in the rabbit are most frequently found along the spermatic vessels and on the epididymis or in the region of the upper pole of the ovary and less rarely in the neighborhood of the main suprarenal glands. On account of hypertrophy they are, of course, more readily detected if the animal survives double suprarenalectomy for a month or more. In five of the fifteen cases we were unable to demonstrate accessory suprarenal tissue. These five animals died of suprarenal insufficiency on the 14th, 20th, 26th, 35th, and 118th day after removal of the second suprarenal. The rabbit (288) that survived 118 days lost approximately 600 gm. in weight in 66 days. At this time a glycerol emulsion of fresh ox suprarenal cortex was added to the diet. This improved his clinical condition and possibly prolonged his life. Another rabbit died on the 25th day. In this animal one 1 mm. accessory suprarenal was found. The remaining nine rabbits survived double suprarenalectomy indefinitely in excellent condition and in all of these either very large or multiple accessory suprarenal glands were found. If further data were needed this is striking evidence of the relation of survival to the presence or absence of accessory cortical tissue.

It is as difficult to perform a complete thyroidectomy in rabbits as it is easy to perform complete removal of the main suprarenal glands. Occasionally one finds a rabbit with the thyroid lobes located rather low so that they are easily detached from the lower border of the thyroid cartilage. When the thyroid lobes are firmly attached to the thyroid cartilage invisible or undetected fragments are often left behind or even a few cells may be broken off in handling the lobes which act as autotransplants. As thyroid tissue is very resistant, easily transplantable, and capable of rapid regeneration a large percentage of rabbits will show gross regenerating thyroid masses if examined a month or more after thyroidectomy.

In twelve of the fifteen rabbits we were able to demonstrate thyroid tissue after death. In two of these only a few thyroid follicles were found by examining serial microscopic sections of the thyroid area. These data concerning accessory and unremoved portions of the suprarenal and thyroid glands are mentioned merely to emphasize one of the difficulties encountered in interpreting experiments involving extirpation not only of these two glands but of any of the so called ductless glands.

The respiratory exchange measurements were made with the modified Haldane open circuit apparatus under constant conditions as regards diet and time of feeding. Objective records of movement were not made. Rabbits for the most part after a period of training remain quiet, otherwise, they have been discarded. We believe that preliminary periods of training and observation are essential. Movement in animals cannot be completely controlled or evaluated. After a great deal of experience we have come to the conclusion that the best safeguards in evaluating the movement factor in heat production measurements in experiments of this nature in animals is obtained by increasing the number of individual observations and by using a two hour observation period. The tables of heat production accompanying the protocols give all of the measurements taken on a given animal and indicate sufficiently well that with these precautions movement as a cause for errors in interpretation may be neglected.

In Table X the number of days during which control or normal heat production measurements for each animal were obtained, is given; also the number of days between thyroidectomy and the removal of the second suprarenal gland and finally the number of days under observation after double suprarenalectomy. The normal metabolic rates show the usual variations for different animals. The decrease in heat production following thyroidectomy also shows great variations, the greatest drop being 31 per cent., the least 10 per cent. and the average 21 per cent. These differences are due to many factors, one of which is clearly the functional capacity and physiological value of the unremoved thyroid tissue. Next, the experiments have been arranged in this table to show the changes in heat production during the first two weeks following suprarenalectomy. In two of these experiments there

was a drop in heat production of more than 10 per cent. below the average level after thyroidectomy alone and in two or 13 per cent. there was a significant rise above the level obtaining after thyroidectomy. In one it was 10 per cent. and in the other 13 per cent. Rises of from 4—6 per cent. were obtained in four others after suprarenalectomy, and while we think they have the same significance as the two in which the rises were higher, they may be considered as possibly within the limits of experimental error. While the rise or fall in metabolism after suprarenalectomy cannot be brought into an exact, graduated relation with the presence or absence of thyroid or suprarenal tissue as determined postmortem, there is a definite general relationship in that those with decreased metabolism after suprarenalectomy showed the least thyroid and suprarenal tissue postmortem, and those with increased metabolism after suprarenalectomy showed the most thyroid and suprarenal tissue. The essential and striking feature of these experiments is the *absence* of a significant rise in heat production in thirteen of the fifteen experiments. In the other two, relatively large amounts of accessory cortical tissue and unremoved fragments of thyroid were found. In suprarenal-ectomized rabbits with intact thyroids a rise of over 10 per cent was obtained in twenty-eight out of thirty-eight experiments or 74 per cent. These data, it seems to us, clearly establish the facts that the presence of the thyroid gland is a factor in bringing about the rise in heat production following partial suprarenalectomy, and the absence of the thyroid is likewise a factor in the failure to obtain a rise after partial suprarenal-ectomy. As pointed out in previous papers, the necessary increase in the discharge of the iodine-containing hormone from the thyroid required to produce the increased respiratory exchange after suprarenal removal, could hardly be explained through stimulation by epinephrin. It therefore appears rather to be in some way dependent upon a weakness of the cortex function. In the operation of double suprarenalectomy most of the epinephrin secreting tissue is, of course, removed, and yet in spite of this loss an increase in thyroid activity occurs in the majority of cases. This suggests that while epinephrin may stimulate the thyroid directly, the withdrawal of cortical control is a much more powerful activator of thyroid activity and the consequent discharge of thyroxin. If, therefore, epin-

ephrin stimulation could be combined with decreased cortical control, a very much more marked increase in thyroid activity and heat production could, in our opinion, be brought about. This would probably simulate what occurs during the Goetsch test and to some extent the conditions usually present in Graves' disease. Aub, Bright and Uridil⁵ have observed that in cats thyroxin causes an increase in heat production, after suprarenalectomy as well as before this operation. We have observed similar reactions to desiccated thyroid in rabbits after suprarenalectomy alone and after thyroidectomy plus suprarenalectomy. We also have some data indicating that suprarenalectomized rabbits may be more sensitive to desiccated thyroid, just as to many other drugs, than are "normal" rabbits. The reaction of the animal with increased heat production is, of course, the same whether the iodine containing hormone is artificially introduced or caused to be discharged from the animal's store in the thyroid gland by the withdrawal of a regulatory or inhibitory influence of the suprarenal cortex. As evidence, however, for or against a thyroid-suprarenal interrelation such observations are irrelevant.

Three of the rabbits (284, 287 and 288) were given 50 mgm. KI, by mouth, in doses of 25 gm. on the eleventh and twentieth days after suprarenalectomy. In two, very distinct and prolonged though small rises, followed by falls in the respiratory exchange were noted. The third rabbit, while not showing the curve noted in the first two, maintained an indefinite rise. This rabbit also happened to show the largest post-suprarenal-ectomy rise in heat production and was the only one showing a rise of more than 10 per cent. Postmortem examination showed considerable unremoved thyroid tissue. Subsequent observations have shown that the failure to obtain a rise in heat production in many of our earlier experiments on rabbits and cats was probably due to exhaustion of the iodine store in the thyroid. Scott³ noted a rise in heat production following the administration of iodine to cats with their suprarenals crippled by ligation or by freezing. In this connection, mention should be made of the fact that suprarenal injury appears to cause a rapid depletion of the iodine store of the thyroid both in rabbits and in cats. The details of these experiments will appear in another paper. Black, Hupper and Rogers⁶ have

reported that feeding an "adrenal residue" to dogs caused an increase in the iodine store of the thyroid.

CONCLUSIONS.

Thyroidectomy abolishes or greatly lessens the rise in heat production which normally follows sufficient injury of the suprarenal function in rabbits.

These nine experiments furnish additional evidence that a thyroid-suprarenal cortex interrelationship exists, which is separate from the thyroid chromophil tissue interrelationship. The nature of this relationship is unknown but the evidence suggests that the suprarenal cortex, as one of its functions, exercises an inhibitory or regulatory control over thyroid activity and when this is sufficiently crippled, as by vessel ligation, freezing, or partial removal, the thyroid automatically responds with increased functional activity, resulting in increased heat production if a sufficient amount of the iodine containing hormone is liberated. There is evidence that single doses of iodine (25 mgms. KI), administered by mouth, increase the heat production in suprarenalectomized rabbits with incomplete thyroidectomies. There is also evidence that sufficient but sub-lethal suprarenal insufficiency in rabbits and in cats causes a rapid loss of iodine from the thyroid.

These observations throw light on the thyroid-sex gland interrelationship known since antiquity and probably have an important bearing both on the etiology of simple goiter and of exophthalmic goiter.

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ADVANCED CHRONIC NUTRITIONAL DISTURBANCES IN INFANCY.

BY KIRSTEN UTHEIM, M. D.

*From the St. Louis Children's Hospital, and the Department of
Pediatrics, Washington University School of Medicine,
St. Louis, Missouri.*

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I. NOMENCLATURE.

The nomenclature and classification of the chronic nutritional disturbances in infancy, have long been the subject of discussion both here and abroad. Different countries have arrangements peculiar to themselves, and it has been noted that nearly every clinic adopts nomenclature as to the etiology, pathogenesis, and treatment of these disorders, according to the ideas of the physician-in-chief.

Chronic nutritional disturbances seem to have been recognized in the very early years of medicine. The Italian physician Hieronymus Mercurialis¹ tells us in the third chapter of his book: "De Morbis puerorum" (1601) that the condition called by him "macie" was recognized by the Greeks under the name *ἰσχυρότης λεπτότης* (leanness), and by the Romans under the name of "macies" "macilentia", "gracilitas", "tenuitas", "macritudo". Soriano² tells us further (1600) that the well-known term "atrophia infantilis" an expression which is still very much used, originated from the Greeks, who seem to have included under this name all diseases, which were accompanied by a wasting of the infant. In the years following we see occasional mention of this condition, which shows that the physicians were cognizant of it but the different authors used different names: Hervieux³ (1862) mentions it as "algidité progressive des nouveau-nés" and Bouchaud⁴ (1864) as "inanition du nouveau-né" because he takes the attitude, that the poor condition of these infants is due to a partial or complete starvation. It was not, however, until 1877 that this condition was made the object of an extensive study when Parrot⁵ published his exhaustive monograph on "L'Athrepsie". This condition seems to have played an important rôle in the pathology of infancy at that time because as he mentions in his introduction, "L'Athrepsie qu'elle soit primitive ou secondaire, mérite par sa fréquence d'être envisagée comme la base de la pathologie du premier âge, c'est ce qui m'a déterminé à commencer par elle".

He uses, here, the word athrepsia to characterize the advanced cases of chronic nutritional disturbances. He has first called attention to the importance of this wasting process, due primarily to a disordered nutrition independent of other disorders, and by this term "athrepsia" designated them as a special group of cases separating them from the larger group called "atrophia infantilis", a wasting process due to any sort of disease in infancy.

Inasmuch as the word "atrophy" had a special significance in pathology he selected a different term "athrepsia", a term which has later been used in France for the advanced cases of chronic nutritional disorders. Other countries, however, did not adopt this expression but still made use of the old term "infantile atrophy". Both terms merely expressed the clinical picture presented by these infants.

As years passed, however, and as the general knowledge of patholo-

gical anatomy, bacteriology and physiological chemistry became greater and interest in the nutritional disorders of infancy grew, a need was felt for a classification which indicated more clearly the etiology and pathogenesis of the conditions concerned. It was felt that by grouping cases according to the etiological factor, a more thorough understanding of the diseases of nutrition would be obtained, as well as a basis for treatment offered.

This leads up to the period of the German authors about 1900.

We are all acquainted with the two classifications originating in Germany during the following 10-15 years:

I. CZERNY-KELLER'S ETIOLOGICAL CLASSIFICATION

1. *Disturbances ex alimentatione.*
 - a. Milchnährschaden (due to excess of milk).
 - b. Mehlnährschaden (due to excess of carbohydrate).
 - c. Barlow's disease (Scurvy).
2. *Disturbances ex infectione.*
 - a. Acute disturbances.
 - b. Enteral infections (sepsis neonatorum).
 - c. Parenteral infections.
3. *Disturbances ex constitutione.*
 - a. Exudative Diathesis.
 - b. Rickets.
 - c. Anemia.
 - d. Neuropathic constitution.
4. *Disturbances produced by congenital malformations.*

This was an entirely etiological classification and was the one used in Germany and other countries in the first years of this century.

The other classification, which came later (1913), is the clinical, etiological one of Finkelstein.

1. *Disturbances due to exceeding the tolerance for food.*
 - a. Mild form.
 1. Bilanzstörung.
 2. Dyspepsia.
 - b. Severe form.
 1. Alimentary decomposition.
 2. Alimentary intoxication.
2. *Disturbances due to Inanition.*
 1. Quantitative.
 2. Qualitative.
3. *Secondary Disturbances due to a Lowering of the Tolerance by infection, heat, etc.*

Both these classifications have been used throughout the world, with more or less criticism and modifications made by different authors. It was felt everywhere that a strictly etiological classification such as Czerny's or a clinical-etiological one such as Finkelstein's was highly desirable and would facilitate treatment. Unfortunately, many of the cases encountered in practice cannot be classified in this

way. The feeling seems to have grown that nature does not follow these systems. Hence, there have been numerous modifications of the two original classifications, modifications which seem to better cover the cases seen and handled in the clinics.

In America, these classifications have been used in a few clinics but have in general not been accepted. In the pediatric clinic of the Washington University, with Marriott as Physician-in-Chief, neither Czerny's nor Finkelstein's classification has been used. It was felt that all the different schemes of classifying these conditions according to the etiology or pathogenesis demonstrates clearly that knowledge of the nature of the nutritional disorders is far from complete. Also, since we have no more definite information about the etiology or the pathogenesis of the conditions with which we are dealing, a classification, based on the clinical picture the infant presents is the only one justifiable. Diseases are classified not only to obtain a view as to their cause and nature, but also, more particularly, to establish a basis for treatment. Intelligent treatment of the patient is, after all, the important problem. The infant must be cured.

The question then arises; will an etiological classification help more in the treatment of the nutritional disorders than one based on the clinical findings, and furthermore, can the picture the infant presents, be taken as an expression of a preceeding etiological factor? This latter seems to be necessary, in order to make an etiological classification justifiable. Both questions must be answered negatively as judging from the clinical material. The clinical picture which an infant presents rarely gives an indication of the etiological factors concerned. An athreptic infant usually presents the same picture, and is treated the same, irrespective of the etiology, whether this be improper feeding, enteral or parenteral infection, or a combination of these factors.

For this reason, the classification in the Washington University has been a clinical one.

NORMAL INFANT.

Acute conditions.

1. Acute diarrhea.
2. Anhydremia.

Chronic conditions.

1. Hypothrepsia.
2. Athrepsia.

A normal infant may, without any acute symptoms, develop hypothrepsia, and if the causative factor still persists the stage of athrepsia. The difference between the two conditions is merely one of degree. Either condition may be present without any diarrhea.

A diarrhea may occur in any stage in a normal infant, as well as in infants where the nutrition has begun to suffer, the prognosis becoming gradually worse with development of the condition.

Any diarrhea may, after shorter or longer duration, give rise to a toxic condition, which is designated in this clinic by the term anhydremia. This name has been used because according to Marriott's idea the symptoms are largely the result of a drying out of the body. The blood concentration is taken as an indication of the degree of desiccation. The symptoms more or less disappear with sufficient water

supply to the body cells. Anhydremia may develop during any stage of nutrition; naturally the prognosis is most severe if it appears in an athreptic infant.

Thus, one picture may very easily develop from the other; an infant who at one time may be considered hypothreptic may later become athreptic and vice versa, and very often an acute condition will develop into a chronic one.

It is very interesting to see that a similar standpoint is taken in Göppert and Langstein's recent book⁶. Langstein's classification is also entirely a clinical one. He differentiates between acute and chronic disturbances. Of the chronic forms, one group includes infants who fail to show a normal gain, but do not present definite symptoms of any special disease, nor is there any striking change in the state of nutrition. These are Langstein's "hypotrophic" infants. Langstein's second group includes infants in whom a definite change in nutrition has taken place, with loss of subcutaneous fat and change in turgor and tonus. The skin is pale and gray and the temperature low. These infants go under the old term "atrophy".

For the acute conditions, accompanied by vomiting and diarrhea the term "dyspepsia" is used. Three types are differentiated according to the nutritional condition of the infant.

Dyspepsia "A": acute diarrhea in the normal infant.

Dyspepsia "B": acute diarrhea in hypotrophic infants.

Dyspepsia "C": acute diarrhea in atrophic infants.

By means of a diagram, he describes the mode of development and frequency of occurrence of the different pictures. Langstein's classification is extremely clear and he emphasizes facts which have practical value.

Finkelstein⁷ in his recent text book on Pediatrics has changed his older classification of 1913, and has also made it more nearly clinical. He emphasizes that the etiological factor is a secondary one.

A review of the French literature of recent years shows that here also, the attempt to force nature into an artificial system has failed. Nobécourt⁸ discusses in one of his recent articles on nutritional disturbances both Czerny-Keller's and Finkelstein's first classification but rejects them both in favor of a purely clinical one. Marfan⁹ takes the same attitude.

The Northern European countries have been using Czerny-Keller's classification, with more or less criticism, in the different clinics for the last 15 years. At the last Northern Pediatric conference held in Stockholm in June, 1921, the classification of the chronic nutritional disturbances was discussed intensively. Some of the members, especially the Swedish Pediatricians, were opposed to etiological grouping and argued in favor of a purely clinical classification. The Norwegians and the Danes wished to retain the old etiological grouping, with some modifications. An attempt to come to an agreement regarding a classification which could be generally adopted was abandoned, as the disagreement was too marked.

Thus, we see that this question, which is of both theoretical and

practical value, has led to widespread discussion. But it now appears that the different pediatric clinics of the world, independently of each other, realize the fact that the attempt of forcing the chronic nutritional disorders into a system based on causative factors must be abandoned, and the more natural grouping, based on clinical manifestations, substituted.

II. ETIOLOGY.

The following discussion of the etiology of athrepsia is based upon observations made in the Washington University Clinic during the years of 1919, 1920 and 1921.

An athreptic condition in an infant will naturally develop secondarily to any severe infection which extends over a considerable length of time, as, in lues, tuberculosis, chronic pneumonia, bronchopneumonia, osteomyelitis, etc. This so-called "secondary athrepsia", which Nobécourt considers as a separate group, is not included in the material of this study. Von Pirquet and Wassermann reactions were done on all hospital cases, as routine, and those with a reaction "positive" have been excluded from the series.

What we are dealing with, here, are infants who, after an acute gastrointestinal upset with vomiting and diarrhea, or without any preceding acute illness of any kind fail to thrive and gain weight. After a shorter or longer period of time they present the well-known picture of athrepsia, with characteristic extreme emaciation.

What is known about the etiology of this condition?

All authors seem to agree that the condition occurs much more frequently in artificially fed infants than in those breast-fed. Of the 102 infants studied in 3 years, all but one have been artificially fed. Feeding is therefore an important factor. It is however, not the sole factor. We have observed development of athrepsia in one of two infants of the same age and under same external conditions and fed in the same way, *e. i.* twins, while the other has developed normally. Besides feeding there is also another factor which enters in, and this is the individual or constitutional factor. As Lesage has expressed it: "*Chaque organisme a sa personnalité, son coefficient de fixation. Chaque nourisson tire une partie différente d'un même aliment*".

We then have two factors to consider: (1), the feeding and (2), the infant itself. A third factor is that of parenteral infections and this stands in close relationship to the two main factors.

In taking up the question of feeding, starvation seems from our material to play the chief rôle in this connection. This starvation may be quantitative or qualitative. It was demonstrated by one of the infants admitted to the hospital in 1922, that a so-called complete or a quantitative starvation can produce the most typical picture of advanced athrepsia.

First child of a 38 years old healthy woman. Birth weight $7\frac{3}{4}$ lbs. Nursed every 3 hours but seemed to obtain very little milk. The infant soon became constipated and would not gain, was constantly fret-

ful and restless, became progressively weaker, lost weight constantly and would not take breast. Was brought to hospital at age of 5 weeks. The most extreme emaciation was present, no cry, temperature subnormal, pulse and respiration very slow. By pumping the mother's breast several times only 5 to 10 cc. of milk could be obtained. It appeared likely that the infant had nursed a practically dry breast from birth. External heat was applied. Two hundred cc. of Ringer's solution was given intraperitoneally and one-half hour later 50 cc. of 10 per cent. glucose was given into the sinus. An immediate improvement was noted. The infant was fed on breast milk and gained rapidly. The feeding was soon changed to one of whole lactic acid milk and the improvement continued until discharge, 6 weeks later.

Such complete starvation is rare, but partial or qualitative starvation is of common occurrence. Throughout this country a very commonly used infant feeding is a sweetened condensed milk mixture. The composition of this mixture is as follows:

TABLE I.

*Composition of Sweetened Condensed Milk (Eagle Brand)**

	Condensed Milk Per cent.	With 6 parts water added Per cent.	With 12 parts water added Per cent.	Per cent. With 18 parts water added
Fat	9.61	1.37	0.73	0.50
Protein	8.01	1.14	0.61	0.42
Sugar	54.94	7.89	4.75	2.90
(Cane, 42.91; Milk, 12.03)				
Salts	1.78	0.25	0.13	0.09
Water	25.66	89.35	94.28	96.09

* Holt: "Diseases of Infancy and Childhood, p. 158, 1918.

The dilution most commonly used is with 12 parts of water. From Table I. it can be seen that this is a feeding containing very much sugar and very little fat, protein and salts. An infant fed on this milk will consequently suffer from a partial starvation of fat, protein and salt. A considerable number of our athreptic infants had been fed at home on this irrational mixture. In 1919 80% of the cases studied, in 1920, 50%, and in 1921 33% had previously been fed on condensed milk. It is quite remarkable that such a feeding has been used so widely. The constant advertising and the fact that sudden gains in weight sometimes occur following this type of feeding (due to water retention) seems however, to have impressed not only mothers but also many physicians. After being fed on such a mixture for some weeks, the infant often develops a diarrhea with vomiting. Other in-

infants become constipated. The weight becomes stationary or falls. Before the mother or physician has finished trying out all the other varieties of proprietary infant foods a more or less advanced picture of athrepsia has developed. The infant is so weak that hospital care seems to be necessary. Such is the history of the majority of our cases. The high carbohydrate content would probably not have done so much harm were it not for the lack of fat protein and salts in the food.

The remainder of the cases had been fed for the most part on fairly good whole milk and barley water mixtures. Over-feeding, which has been so much emphasized by the pre-war German School does not seem to be a factor in our cases.

The question arises as to the cause of the development of athrepsia in these cases fed on a customary whole milk formula. This question will necessarily lead us into the old and well known discussion of the harmfulness of cow's milk to certain infants. In this connection every constituent in the cow's milk has been accused of being harmful. A variety of theories have been advanced.

Biedert's theory based on the harmfulness of protein was soon given up, when it was seen that nutritional disturbances often cleared up by increasing instead of decreasing the protein in the milk. There is furthermore no essential difference between the end products of digestion of a homologous and a heterologous protein. Each must be broken down to its simple compound before being built up to body protein.

Czerny's theory based on fat as the harmful factor has been viewed with great criticism since it has been found that the difference between breast milk and cow's milk fat is very slight.

Finkelstein's theory of the toxicity of cow's milk whey has received little support since a recent investigation by Lichtenstein and Lindberg¹⁰ has shown that the original whey exchange experiments done by L. F. Meyer¹¹ could not be confirmed.

Marriott¹² thinks that one of the main differences between breast milk and cow's milk is the different buffer values. Cow's milk has a much higher buffer value than breast milk and requires 3 times as much hydrochloric acid as human milk, in order to bring the acidity of the stomach contents to the optimum hydrogen ion concentration for gastric digestion. He assumes therefore that it is beyond the functional capacity of certain infants to secrete this extra amount of acid, and as a result, the bacterial inhibition and rennin action in the stomach occurs only to a slight degree. Furthermore secretin formation, and the hormone stimulation of the pancreatic juice and biliary secretion will be diminished. This naturally will result in a slowing of the passage of both the stomach and upper intestinal contents and provides a good medium for the invasion of *B. coli* into the upper intestinal tract.

It seems to be evident, from the work of Bessau and Bossert¹³ on living infants, that such a *B. coli* invasion of the upper intestinal tract does occur in infants suffering from nutritional disorders. A recent work by Bessau, Rosenbaum and Lichtentritt¹⁴ points in the same direction, namely, that it is the stagnation of food in stomach and

upper intestine, with secondary coli invasion, which is responsible for the failure of cow's milk in some cases. They, however, claim that the stagnation is due to the protein in the cow's milk. It was found that both the quantity and quality of cow's milk protein was important as the emptying time of the stomach was slower than that for breast milk, even with the protein reduced to the amount occurring in human milk. When, however, the cow's milk was previously subjected to peptic digestion this difference in the emptying time disappeared. Even this seems to support Marriott's point of view inasmuch as the stomach contents are more acid as a result of the preceding peptic digestion. This hastens the emptying process.

Another point of difference between breast milk and cow's milk, which has very recently been considered, is the fact that the sugar percentage of the stomach content varies considerably, according to whether breast milk or cow's milk is fed. Hoffman and Rosenbaum¹⁵ found that the sugar curve for cow's milk fell considerably in the stomach content, throughout the period of two hours, whereas for breast milk it remained unchanged until the content was emptied into duodenum. The cause was found to be the different protein content of the two varieties of milk and the explanation was that an increased secretion took place when cow's milk was present, until the protein percentage became the same as that for breast milk.

These recent findings seem to demonstrate that there is a definite extra effort required of the organisms fed on cow's milk, as compared with the effort expended by those fed on human milk.

While most of the artificially fed infants seem to be capable of this extra effort, other infants do not possess the necessary vitality or reserve energy, and as a result a stagnation in the stomach and upper intestinal tract occurs. An invasion of *B. coli* takes place with the development of fermentation, resulting in an acute diarrhea. This necessarily effects the nutrition of the infant. After such an attack the infant is left with still less vitality and reserve energy and we have a vicious circle.

In the theory outlined above, the assumption is made that infants with lack of reserve energy will become the victims of the initial phase of a nutritional disorder. That is, we are apparently forced to assume the presence of a constitutional factor. This brings us to a consideration of the infants' constitution.

It is well known that Czerny¹⁶ assumes a constitutional factor in the development of athrepsia. He thinks that these infants are either suffering from an "exudative diathesis", are the children of neuropathic parents with extreme nervous irritability of the intestinal tract, or, are children with hydropic constitutions who show difference in water and salt retention from normal children.

It is very easy to take refuge in a constitutional factor when our positive knowledge is exhausted, but it is always with a feeling that something may have been overlooked. The more actual knowledge we acquire about the processes going on in the organism, the less will we talk about the constitutional factor. Authors do not seem

to agree what is actually meant by a constitutional factor in development of disease. Is it inherited weakness, or is it a weakness produced by the more or less unfitted environment?

It is certainly a very difficult matter to determine whether or not a constitutional factor plays a rôle in this or any kind of disease as long as the conception of the term constitution is not a definite one. It was thought, however, that some idea might be gained by considering the infant's family, gathering information as accurately as possible about brothers, sisters, parents and grand-parents of the infant. The family histories of our athreptic infants were looked into. It was found that for the year 1919 only 6 out of 33 cases (18%) show a positive family history of any form of constitutional or chronic weakness. Of these six infants three were fed on condensed milk; the others had been fed properly. For the year 1920 only seven out of forty-one cases (17%) showed a positive family history; of these, two had been on condensed milk. For the year 1921 six out of twenty-seven cases (22%) showed a positive family history; of these only one had been properly fed. From this summary it is seen that of the one hundred and two athreptic infants seen in these three years only nine infants who had been properly fed gave a positive family history.

From the histories of our cases, it was furthermore evident that in the majority of the patients acute gastro-intestinal disturbances with vomiting and diarrhea played a prominent rôle in developing the picture. Of the infants seen in 1919 66%, in 1920 56% and in 1921 63% had had acute attacks of diarrhea.

An attempt has been made to follow these infants after discharge from the hospital. It has been impossible, of course to have complete records of all infants, on account of the families moving from the city, but of the infants we have been able to follow, it has been interesting to note that about 50% of those discharged from the hospital have developed as perfectly normal children. One or two years after discharge from the hospital it has been impossible, from the appearance of the child to suspect the earlier condition. They do not differ from the rest of children in the family. On examining them more thoroughly, they sometimes show slight signs of rickets but no signs of any other disease. The definite impression was gained that once the organism has survived the first difficult period, it developed further in a perfectly normal way.

It is a well recognized fact that structural abnormalities of the body may lead to athrepsia. The most common of the abnormalities are malformation of the heart, central nervous system and genito urinary tract. Such anomalies may not be detected during life and yet be entirely sufficient to account for the condition. Doubtless, a fair number of the cases in which constitutional weakness is diagnosed, belong to this class.

It seems then, from our material that the constitution may in some cases be the only factor which will explain the development, but in the great majority of cases there are evidently other factors which are the determining ones. We have mentioned the feeding, but in cases

where the feeding has been a proper one, and where there is nothing definite which points towards a constitutional weakness, then what is responsible for development of the condition?

Now we have come to the third point which ought to be mentioned in the etiology of this disease, that is, the parenteral infections. They are taken up here rather than under the symptomatology because we think that the parenteral infections in these infants are just as often the cause of the poor nutrition as they are the result. It is believed that during a parenteral infection a normal artificially fed infant has less of the above mentioned reserve energy. This results in a stagnation of food, as has been previously mentioned with coli invasion of the upper intestinal tract. This initiates a nutritional disorder. The parenteral infections have doubtless been overlooked by some observers, and the erroneous conclusion has been drawn, that the infant's constitution was at fault. This is especially likely to be the case when such infections occur without temperature reaction. A parenteral infection may leave the infant constitutionally weak, but the infection is, nevertheless, the original factor. These infections, sometimes multiple, especially pyelitis and otitis media are extremely common in these cases. 65% in 1919, 56% in 1920, and 70% in 1921 of all athreptic infants in the hospital.

The different vitamins may play an important part in the etiology of athrepsia. As this cannot throw any light upon the subject, they are not discussed in this paper. Further study along this line may reveal important facts.

Based on the material in this clinic, it is believed, then, that in the etiology of athrepsia, feeding is the main factor, a quantitative and especially a qualitative starvation being responsible for the development of most cases, that the constitutional factor is of less importance and that the parenteral infections will often contribute in developing the picture.

III. SYMPTOMATOLOGY.

Every pediatrician is so familiar with the clinical picture of athrepsia that I shall not attempt a full discussion of the symptomatology. A few symptoms regarding which there have been disagreement of opinion will be considered as the material from this study throws some light upon the matter.

The first symptom we wish to discuss is the skin color of these infants. It is well known that as the condition of an athreptic infant grows worse the color of the skin becomes more and more pale with a distinctly gray tint. It is usually stated in the textbooks that the blood counts are in striking contrast to the extreme degree of pallor. Is there an anemia present or not? In order to answer this question we have to consider the total blood volume as well as the composition of the blood. We know from Marriott's¹² finding that the total blood volume is diminished in these infants. There is very little information in the literature relative to the blood count in athrepsia. Schlesinger¹⁷ found that the hemoglobin and red cells were diminished in the early stages

of threpsia. The white cells were often diminished. Hyperleucocytosis was unusual.

Cell count and hemoglobin determination were done on twenty-four of our athreptic infants, all in a rather severe stage. As comparison, will be taken a serie of determination done in 1917 in Copenhagen on 75 perfectly healthy infants. The average findings were as follows: The high hemoglobin content of approximately 110 (Sahli) directly after birth, falls, within the first two months of life, to 80. From then to six months of age it drops to 70, from then until one year it is between 60 and 70 and in the second year around 65. The red cells remain between five and six million. White cells average twelve thousand..

TABLE II.

*Blood Count and Hemoglobin Determination of
Athreptic Infants.*

No.	Age.	Weight	Red Cells	White Cells	Hemoglobin
1	6 wks.	2,800 gms.	4,044,000	9,800	70
1	7 "	3,150 "	4,844,000	12,200	69
2	6 "	3,000 "	4,832,000	13,400	75
3	10 mo.	3,700 "	2,770,000	6,600	50
4	5½ "	4,270 "	4,700,000	14,000	55
4	5½ "	4,230 "	4,796,000	13,200	56
5	3 "	3,560 "	3,736,000	12,600	64
6	3 "	3,440 "	4,680,000	12,000	60
7	3 "	3,560 "	4,468,000	15,200	70
7	3½ "	4,130 "	3,916,000	16,800	68
8	6 wks.	2,590 "	3,672,000	15,800	60
9	3 mos.	1,930 "	3,920,000	14,000	45
10	2 "	2,425 "	8,216,000	14,600	70
11	2 yrs.	7,510 "	4,088,000	15,600	46
12	11½ mos.	5,600 "	4,936,000	12,400	73
13	1½ "	2,300 "	4,720,000	11,800	56
14	2½ "	2,415 "	4,288,000	12,900	54
15	2 "	2,440 "	3,116,000	11,600	51
16	4 "	2,440 "	4,184,000	12,000	66
17	6½ "	3,620 "	3,292,000	12,400	60
18	9½ "	5,838 "	5,296,000	11,200	56
19	14½ mos.	5,800 "	2,660,000	10,520	60
20	3 wks.	2,000 "	3,584,000	15,800	59
21	9 "	1,842 "	4,376,000	9,600	52
22	9 "	2,443 "	3,848,000	8,000	60
23	1½ mos.	3,150 "	4,144,000	10,100	55
24	3½ "	3,320 "	5,210,000	13,500	60

From Table II. it is seen that with one exception (No. 10) the red counts and hemoglobin are slightly below the normal. Were it not for the diminution in the total blood volume of these infants the counts would doubtless be lower. There is, then, both an actual and relative anemia present in these cases. The changes however, both in the

relative and absolute amount are not marked and will possibly not explain the extreme gray pallor present. There must, in addition, be some circulatory changes, with a withdrawal of the blood from the periphery, and especially from the skin capillaries. That such a change is present has been shown and will be discussed in the next section. The average white cell count seems to be slightly above the usual normal figures, but in the presence of infection there is not a marked leucocytosis.

The next symptom which we will mention is the enlarged inguinal glands. Fröhlich¹⁸ was the first one to call attention to these glands as a symptom and a result of preceeding chronic infections, particularly in the intestinal tracts. All the athreptic infants studied have shown distinct enlargement of the inguinal glands. The glands are usually rather firm, not confluent, and not tender on pressure. Any general glandular enlargement has not been present.

The duodenal ulcers first mentioned by Parrot, and later described more thoroughly by Helmholz¹⁹ have been looked for in all autopsies done⁽²¹⁾ but in no case were they found. In two cases there was bloody vomitus on passage of dark brown colored stools just before death. Unfortunately, an autopsy could not be obtained in either case. Helmholz found a duodenal ulcer in eight of sixteen cases of "pădatrophie" which came to autopsy.

The observations of Schindler²⁰ of the dirty-brown grayish color of the iris due to a pigment decomposition on account of breaking down of hemoglobin has not been confirmed on the cases seen here.

Loose stools have, as mentioned, been common. On the other hand it is not unusual for an infant, fed on high sugar mixtures of condensed milk, to be more or less constipated. This confirms the fact that even a very high sugar feeding may be kept up over a considerable length of time without necessarily producing a diarrhea.

As mentioned the parenteral infections have been extremely common. Pyelitis was present in nearly all cases, especially those with a preceding diarrhea.

IV. PATHOGENESIS.

1. *Literature on Pathogenesis.*

One of the earlier theories of athrepsia considered the condition as the result of an actual atrophy of the intestinal tract. On account of the anatomical changes, which several authors found, a real atrophy of the epithelial cells with a disappearance of the so-called Paneth cells, the function of the intestinal tract would be so lowered that the nutrition of the infant would suffer considerably.

Heubner's²¹ complete anatomic examination of the intestinal tract made it clear, however, that such changes as have been earlier described were not pathological, but were present even in a normal intestinal tract merely due to post mortem changes.

It was then thought that the dissimilation process was incomplete in these infants mostly on account of the lack of enzymes in the upper

intestine. Reeve-Ramsey²² and Rosenstern²³ both found that pepsin secretion was somewhat diminished in athreptic infants. It was not felt, however, that this was enough to explain the marked changes in the nutrition in these infants.

Then Heubner²¹ propounded his theory on the pathogenesis of athrepsia from the standpoint of the energy balance. Based on a metabolism experiment on an athreptic infant he comes to the conclusion that a negative energy balance occurred in the infant on account of lack of absorption in the intestinal tract. In other words, that there was a partial inanition as a result of absorption of an insufficient amount of food.

Czerny looks upon the condition from an entirely different point of view. He assumes that these infants have a low assimilative power for the fat, and as a result, fatty acids are formed in excess in the intestinal tract. These fatty acids, according to Czerny, require alkali for neutralization and the alkalis are taken from the tissues and excreted into the gastro-intestinal tract. In the presence of diarrhea it is the sodium and potassium which are thus secreted and lost, and in the presence of constipation, with soap stools, the calcium salts. In order to make up for the alkali deficit caused in this manner, ammonia is formed in the body and excreted in the urine. According to this theory the essential factor in the pathogenesis of the disturbance is the condition of demineralization of the body. On account of this mineral loss it is assumed that the cell structure and the tissue composition is altered, and that if a sufficient loss takes place, the normal cell function will be so disturbed that the building up of new tissue is impossible, even if the processes in the intestinal tract are restored to normal.

Czerny's theory is based upon the experimental work of Steinitz and Keller. In 1897 Keller²⁴ examined eleven infants suffering from acute and chronic gastro-intestinal disturbances, and found in all except one a considerable increased ammonia output in the urine. He comes to no conclusion as to whether this high ammonia excretion was due to an increase of acid in the body, or to an impairment of the function of the liver for the synthesis of urea. In a later work Keller²⁵ attempts to show that there is no disturbance of liver function in these infants.

The other work on which Czerny's theory is based was done by Steinitz²⁶ (1903). He found that a large amount of fat in the feeding increased the ammonia output in the urine. With an increased loss of alkali through the intestine, and a corresponding decreased loss in the urine. The theory of Czerny and Keller has met considerable opposition. Pfaundler²⁷ was one of the first to criticize this. He found an increased ammonia output in the urine of athreptic infants but not as much as was found by Keller. Pfaundler examined the oxidizing power of the liver of these infants post mortem and made observations which led him to believe that there occurred a degeneration of liver tissues with resulting lack of power to synthesize ammonia to urea. Pfaundler considers the disturbance in the intestinal tract merely secondary to

primary disturbances in the body cells, which profoundly affected the intermediary metabolism.

In 1906 Meyer and Langstein²⁸ stated, without giving the exact figures, that they had never found an increased ammonia output in the urine of athreptic infants and denied that acidosis played any rôle in the development of the condition.

Finkelstein⁷ does not agree with Heubner's point of view that the whole picture of athrepsia can be explained on the basis of inanition as a result of lack of absorption from the intestinal tract. The different weight curve of the starved child and the infant with athrepsia is taken to indicate that there are different processes going on. In a starved organism the weight loss is slow, and in an athreptic more rapid. He thinks that this very rapid weight loss can be explained only on the basis of a pathological loss of water, and assumes that these infants suffering from athrepsia are incapable of retaining the necessary water in the tissues. The water combining power of the different body cells has been lost. As a result of this loss of power to keep water in the tissues, a negative nitrogen and alkali balance will occur, which finally becomes fatal. He further believes that the inanition, as a result of the fermentation of carbohydrates and the rapid passage through the intestinal tract, with a caloric loss, will help to explain the marked malnutrition in these infants. He assumes that most of the cases with athrepsia have a constitutional hydrolability, but that the picture may develop in an infant with a normal constitution as a result of starvation or underfeeding, or as a result of a chronic infection. He believes that intestinal disturbances alone will probably not give the picture, except very rarely. He does not agree with Czerny that the fermentation, with the formation of lower fatty acids, is the cause of the negative nitrogen and alkali balance. The fermentation of carbohydrate in the intestinal tract will have the same effect as carbohydrate deprivation; a lack of retention of water, which results in a lack of retention of nitrogen and alkali.

While both Czerny and Finkelstein consider demineralization as the essential in the whole picture, according to the two authors, the mode of its development is different. While Czerny considers it merely a neutralization process as a result of fermentation in the intestinal tract, Finkelstein considers it as a result of cell injury.

Marriott¹² views this from another angle. He considers athrepsia as a result of a prolonged period, during which food absorption and utilization is less than the caloric output, or in other words, the result of a prolonged negative energy balance. He emphasizes that once the condition is established there is a diminution in the volume and the volume flow of the blood, which results in an inability of the infant to utilize suitable food given in reasonable amounts. He considers the slight degree of acidosis sometimes observed as a result, but in no way a cause of the condition.

I have taken up the pathogenesis of athrepsia for further investigation because there seem to be important factors in the development of this condition, first marked by Marriott, and these factors perhaps ex-

plain some of the symptoms in this condition. These are the physical and chemical changes of the blood and its circulation in these infants and the result of these changes.

The weight loss, is, perhaps the most striking symptom. As the weight loss is always in near relation to the water content and water metabolism of the infant, it was thought important to first investigate the water metabolism of these infants.

2. *Changes Taking Place in the Water Metabolism of Infants During Nutritional Disorders.*

Freund²⁹ was, so far as I know, the first to draw attention to the fact that the irregularity of the curve of the artificially fed infant can only be explained by the ever changing water content of the body and not by the variable content of dry substances.

The water content of the body is not constant, in fact it varies a great deal, and the younger the individual the greater the variation.

It is influenced by two main physiologic factors:

1. Age of the individual.
2. Character of the food.

Besides these two factors must be mentioned diseases which influence the water content by increase or decrease of the body excretions.

As far as the age is concerned, Bezold³⁰ in 1857 studied this question thoroughly, and came to the conclusion that there was a decrease of the water content and volatile constituents from the embryonic period to the height of full development.

The other factor is the feeding. The importance of this has been noted by Bischoff and Voit³¹. In 1860 they performed an experiment on a dog, fed exclusively on bread for a period of 41 days. They found that although the nitrogen loss corresponded to 3.713 gm., the animal lost only 351 gm. in weight and concluded that water retention must have taken place. Further, Bischoff and Voit³² fed cats exclusively with bread and found the water content of the brain and muscles to be from 3 to 4 per cent. higher than in control cats fed with mixed food. According to Zuntz, Loewy, Muller and Caspari³³ this is due to the fact that when glycogen is stored in the body it takes with it three times its weight of water. Rubner's³⁴ statement that the water content in the body depends exclusively on the simultaneous fat content, has been disproved by different authors. Steinitz³⁵, Hoesslin³⁶, Forster³⁷ and Chaniewski³⁸ all showed that the water and the fat content of different organs are not always inversely proportional to each other. Weigert's³⁹ work on dogs in 1905 shows very plainly that the water content of the body depends not only on variations in the fat content, but also on the amount of fat free substance present.

The experimental work done to date seems to show there are two physiologic factors which determine the water content of the body, viz; (1) the age; (2) the feeding.

In passing to a consideration of the infant's organism it is clear that in order to get an idea of the water content the ideal way would be

to make a complete study of all the organs which are especially known to be the water repositories. Such a procedure is, of course, impossible during life. The only tissue which is available for investigation is the blood. Many examinations of this tissue have been made.

Since the work of Audral and Gavaret⁴⁰ in 1842 and immense amount of literature on this subject has appeared. Most of the work, however, has been performed on adults and only during the past ten years have pediatricians paid especial attention to the topic.

The first question which arises is whether or not it is possible to draw conclusions concerning the water content of the body, as a whole, from an examination of the blood alone.

For a long time it has been believed that the blood did not change its concentration at all, that under different conditions it tended to keep its composition constant, and that when necessary, water from the different water depots could be drawn upon to supply any deficit. Magnus⁴¹ for instance, thought so and with him Plehn⁴² and Engels⁴³. Panum⁴⁴ held a different opinion and Tobler⁴⁵ was able to demonstrate in his experiments on dogs, on which he produced a water loss by diarrhea, that the water loss in the blood amounted to several per cent. Grawitz⁴⁶ has also observed a marked concentration of the blood as a result of water loss from various causes. At the same time he calls attention to the fact that these changes often take place so quickly that they may be overlooked when examinations are made too late. He further states that the blood should not be considered as an isolated organ of invariable volume but as part of the lymphatic system with which it is intimately associated.

In the last 10 years several studies have been made on the water content of infants' blood. The main purpose has been to determine the relationship of variations in body weight to fluctuating water content in the blood, and thereby in the whole organism, and especially to follow the water metabolism during acute diarrhea and vomiting. Various methods have been used by different authors. The methods have been: (1) specific gravity determinations, (2) direct determination of dry substances; (3) chemical determination of protein; (4) freezing point lowering; (5) determination of conductivity and of (6) viscosity. These methods either require so much blood, or are so time-consuming that they are not well adapted for blood examinations on infants who can stand but little loss of blood, especially when the determinations have to be done daily. These difficulties are overcome by the use of the refractometric method, first used by Strubell⁴⁷ i.e., the determination of the protein concentration of the blood by refraction. It has been shown by earlier workers that the refractive index of the blood serum may be regarded as a function of the protein. It is, of course, only an approximate estimation, because the angle of refraction is not affected by protein alone. Protein does, however, change the index of refraction much more than the other solid constituents of the blood serum. Salts and other substances which have to be considered, show with some exceptions, a rather constant concentration and also constant refractometric value which has to be

subtracted. The error due to changes of these substances does not exceed 0.3 per cent. of the calculated protein content. The refractometric method gives a good approximate result though no conclusions should be drawn from very small changes.

The first work of any importance performed on infant's blood was done in 1909 by Emil Reiss⁴⁸ who made use of the refractometric method. He is, as far as I know, the only one who has examined normal infants at different ages. He found a constant increase from birth up to the tenth or twelfth month when the concentration reaches that of the adult. Furthermore, he examined nineteen cases of different gastro-intestinal disturbances in which he found a special relationship between the weight curve and the protein concentration of the blood. Most of his patients were suffering from acute diarrhea or vomiting, and showed a high concentration of the blood, which under treatment fell to normal.

In 1911 Lust⁴⁹ using the method of determining the dry substances in the blood, obtained results very similar to those of Reiss. His material consisted of twenty cases and one of his conclusions was that in the chronic intestinal disturbances the water content of the blood does not differ from that of the blood of normal infants. In 1911 Salge⁵⁰ found a low protein concentration in 2 athreptic infants using the refractometric method. Behrend and Tezner⁵¹ examined the blood of infants with alimentary weight changes in regard to refraction, viscosity, freezing point lowering and conductivity, but found no special relationship between the changes in the blood concentration and the weight. In 1914 Lederer⁵² published a paper on the same subject. His method was the determination of the total dry substances of the blood by weighing on Kuhlmann's scale. He examined five normal infants and thirteen infants with chronic intestinal disturbances and found in most instances a high water content of the blood.

Recently Marriott and Perkins⁵² using the refractometric method found a high concentration of the blood in acute diarrhea, (Fig. 1) and a low protein concentration in the chronic nutritional disturbances (athrepsia).

As a summary of the literature, it may be stated that most authors have found that the acute nutritional disturbances with diarrhea and vomiting are usually followed by a concentration of the blood. Only in the discussion of chronic intestinal disturbances do the opinions differ markedly.

3. *Observations on Protein Concentration of Blood Serum in Normal and Athreptic Infants.*

In order to be able to compare results on athreptic infants the normal blood protein was first determined. The blood examined was taken from the infant's heel, without any pressure, two or three hours after meals, and read with the refractometer. Earlier work has shown the influence of food intake on the blood concentration. Schmaltz⁵³ showed, with the capillary pyknometer, that the specific gravity usually drops after meals and returns to normal half an hour after the

last meal. Hammerschlag⁵⁴ showed with the same method that the difference could be noted in from fifteen to thirty-five minutes after meals, but this has disappeared in from forty-five minutes to one hour after the meal. Lust⁴⁹ found that the fluid intake raised the water content of the blood as much as from 0.2 to 0.4 per cent. In view of the foregoing it would seem likely that if blood were taken from two to three hours after meals, the influence of the meal would be eliminated. The results appear in Table III.

TABLE III.
The Blood Protein of Normal Infants.

AGE	No. of infants examined	Average Protein Percentage	AGE	No. of Infants Examined	Average Protein Percentage
1 day	14	6.25	3 months	1	6.06
2 days	12	5.8	3½ "	2	6.33
3 "	12	6.33	4 "	2	6.55
4 "	9	6.63	4½ "	3	6.35
5 "	13	6.59	5 "	4	6.90
6 "	9	6.25	5½ "	1	6.12
7 "	8	6.83	6 "	2	6.34
8 "	4	6.27	8 "	1	6.12
9 "	7	6.33	11 "	1	6.87
10 "	3	6.19	13 "	3	7.00
11 "	4	6.03	13½ "	1	7.63
12 "	4	6.26	15 "	1	7.42
13 "	3	6.47	16 "	3	7.63
14 "	3	5.90	17 "	3	7.63
16 "	1	6.12	20 "	1	8.71
1 month	3	6.29	2 years	2	7.86
1½ mos.	3	6.28	2⅓ "	1	8.06
2 "	2	6.32			

It will be seen that the protein content during infancy varies from 6 to 6.5 per cent. and remains at this level until the tenth or eleventh month, when it begins to rise. By the fifteenth month it has reached the adult level.

The results are expressed graphically in Fig. 1. (for purposes of comparison the results obtained by Marriott and Perkins on infants suffering from acute diarrhea with toxic symptoms are included in the chart.)

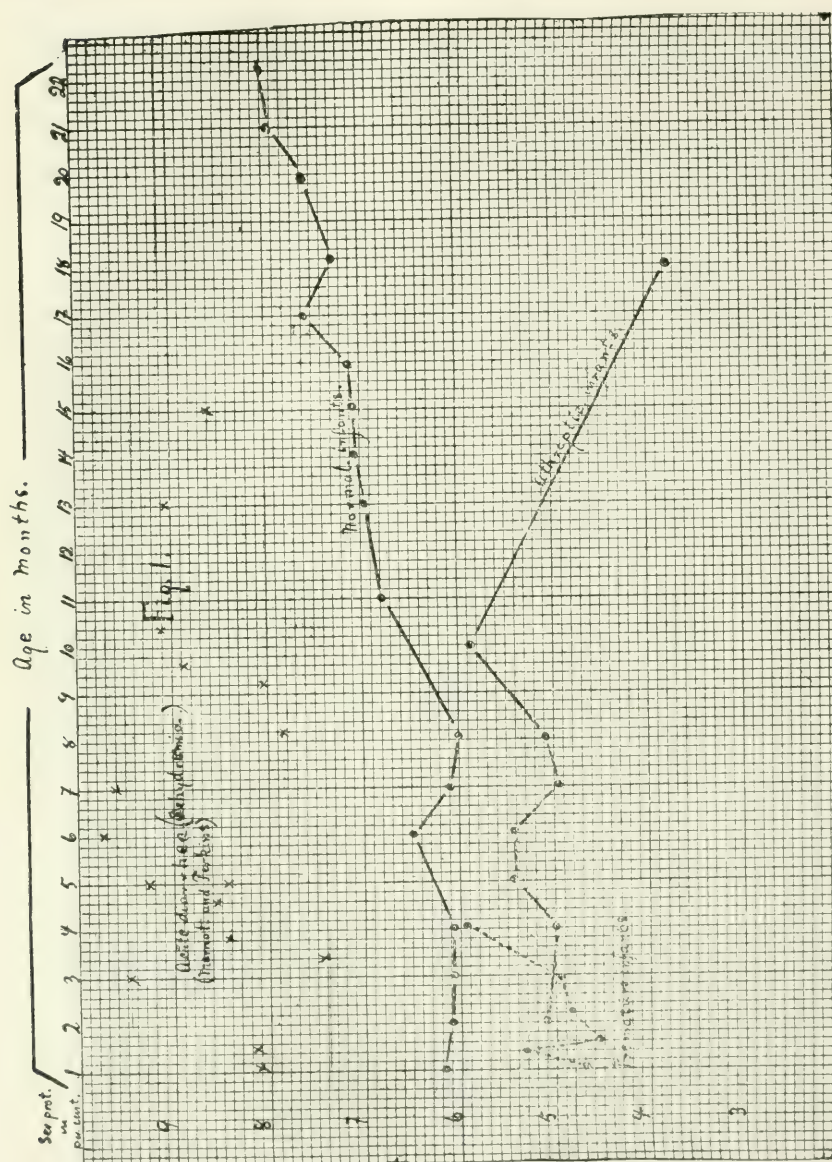


FIG. 1.

We see here the influence of one of the factors mentioned in the beginning of this paper, namely the age. The old, well known fact is once more stated. The younger organism contains relatively more water than the mature organism.

Showing percentage Serum protein in normal, athreptic and premature infants.

If we could follow the infant back into intrauterine life we would, according to Bezold³⁰ find a still higher water content. This explains very easily the high water content of premature infants which has been found, as may be seen in Table IV. Premature infants do not acquire a normal water content before three months of age, (Fig. 1.)

TABLE IV.
Blood Protein of Premature Infants.

Number	A G E	Average Protein Percentage	Number	A G E	Average Protein Percentage
1	1 day	4.91	13	3 weeks	5.03
2	1 "	4.16	14	5 "	4.16
3	2 days	3.94	15	5 "	5.42
4	3 "	5.13	16	6 "	4.47
5	3 "	5.13	17	6 "	4.42
6	1 week	5.78	18	7 "	5.03
7	2 weeks	5.05	19	7 "	5.23
8	2 "	5.68	20	9 "	5.68
9	2 "	5.68	21	10 "	5.90
10	3 "	4.59	22	3 months	6.34
11	3 "	4.49	23	3 1/4 "	6.77
12	3 "	4.26			

As far as the physiologic daily changes are concerned, there has been little done. Rusz⁵⁵ who examined ten infants, found the protein content (refractometric method) to decrease steadily during the day, and found the lowest value in the evening. This he believes to be the result of the fluid intake during the day. Further, he found such a high difference between the morning and evening figures that he believes no conclusions can be drawn regarding pathologic changes. My findings do not agree with his.

TABLE V.
Blood Protein of Infants Showing the Results of Several Examinations Upon the Same Day.

No.	8 A.M. Per cent	12 Noon Per cent	8. P.M. Per cent	No.	8 A.M. Per cent	12 Noon Per cent	8. P.M. Per cent.
1	7.63	8.28	8.38	8	6.34	6.22	6.34
2	6.55	6.98	6.77	9	6.34	6.00	6.55
3	4.47	4.26	4.25	10	5.90	6.00	6.65
4	6.12	5.47	5.90	11	8.25	7.50	7.52
5	6.34	6.22	6.55	12	5.78	5.90	5.78
6	6.87	7.08	7.10	13	7.08	7.20	6.55
7	7.85	7.85	8.28				

Table V. shows that of the thirteen infants examined six showed the highest protein in the evening, two no change, three lowest in the middle of the day, and only two lowest in the evening. And, furthermore, the daily difference never exceeded 0.75 per cent. It is thus seen that the daily physiologic changes are so slight that it is justifiable to draw conclusions from larger deviations in pathologic conditions.

When we now consider the protein concentration in athreptic infants, Table VI. and Fig. 1 show results obtained on the blood serum of a number of these infants.

TABLE VI.
Blood Protein of Athreptic Infants.

Number	A G E	Protein Percentage	Number	A G E	Protein Percentage
1	1 month	5.78	20	3 months	5.68
2	1 "	5.13	21	3 "	5.47
3	1 "	5.30	22	4 "	5.31
4	1½ months	4.59	23	4 "	5.90
5	1½ "	5.68	24	4 "	5.57
6	1½ "	5.57	25	4 "	5.90
7	1½ "	5.38	26	4½ "	5.57
8	2 "	4.37	27	4½ "	5.49
9	2 "	5.68	28	4½ "	5.30
10	2 "	5.31	29	5 "	5.47
11	2 "	5.90	30	5 "	5.25
12	2 "	4.69	31	5½ "	5.80
13	2½ "	4.69	32	5½ "	5.57
14	2½ "	4.69	33	6 "	5.25
15	2½ "	4.81	34	6 "	4.67
16	3 "	5.78	35	7 "	5.32
17	3 "	4.91	36	9 "	6.16
18	3 "	5.68	37	18 "	3.94
19	3 "	5.78			

By comparison with Table III. it will be seen that the average protein content of the serum of these infants is distinctly lower than that of normal infants. In connection with what has been mentioned earlier we may conclude that these infants have a higher water content of the blood than normal infants. The low protein findings in my cases may be explained partly on the basis of the preceding feeding, which in the majority of cases was extremely low in protein, and partly as a lack of power on the part of the organism to build up its normal blood protein. I will call attention to the fact that the majority of these cases have been fed on the above mentioned sweetened condensed milk. Franke and Stolte⁶⁶ in their studies of liver substance from infants suffering from "Mehlnährschäden" found an abnormally high water and salt content.

Fig 2 and 3 show the variation in protein concentration during different stages of nutrition.

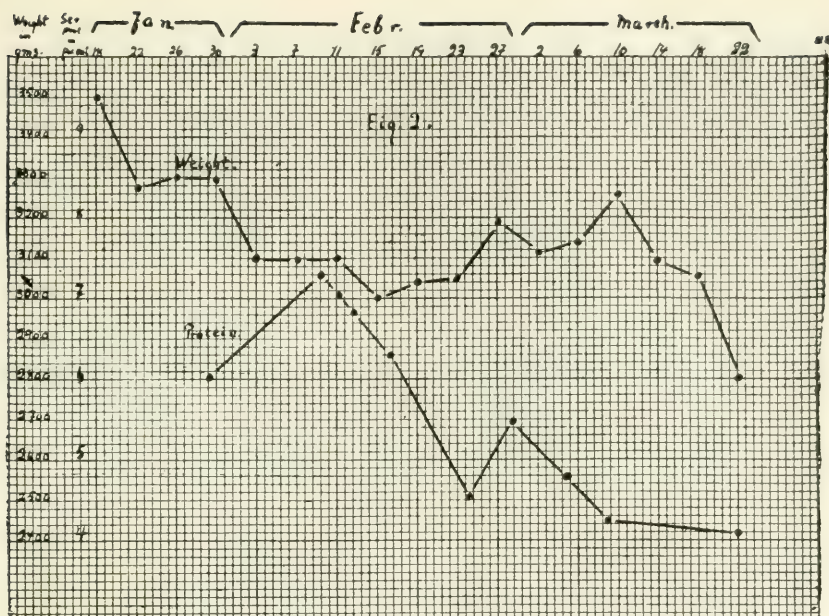


FIG. 2
Showing decrease in Serumprotein in an infant with falling weight curve

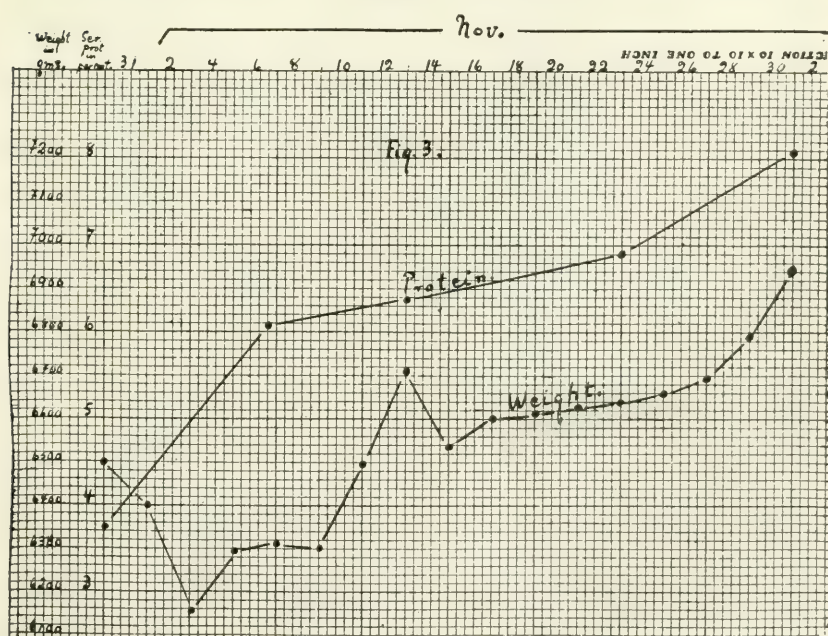


FIG. 3
Showing increase in Serum protein in an infant with increasing weight.

Fig. 2 is a curve from a patient admitted on account of gonococcus infection of the eyes. The blood protein on admission was normal, 6 per cent. The baby developed an ileocolitis. The blood protein went up to 7.20 per cent. Diarrhea stopped and blood protein went down to nearly normal, but the baby would not gain and went over in an athreptic stage with drop of protein to 4.37 per cent.

Fig. 3 shows the results from an infant who was recovering from a nutritional disturbance.

After having had indigestion for three months, the child was admitted very emaciated, a typical picture of athrepsia with blood protein 3.94 per cent. In the hospital the child recovered very rapidly. There was an increase in the protein content of the blood serum which was 8.06 per cent., when the child was discharged, in excellent condition, after having been fed on the high caloric whole lactic acid milk, a food especially suitable for these athreptic infants (Marriott⁶⁶).

Both cases seem to indicate that there is a lack of power on the part of the organism to build up protein during the low athreptic stage.

As both infants, however, before admission had been fed on sweetened condensed milk, the food, also, plays a part in these cases even if the blood protein in the first case was normal on admission.

Earlier and recent investigations seem to point in the same direction, that the organism of these athreptic infants contains more water than a normal one. Ohlmüller⁵⁷ found, by analysis of the organs from infants, that the normal child contains 60 per cent. water and 40 per cent. solid material, while an athreptic one contains 74 per cent. water and only 26 per cent. solids, a fact which he ascribed to the loss of fat in athreptic infants. Von Hösslin⁵⁸ has shown an increased water content of the voluntary muscles and the heart muscle in diseases combined with emaciation. The fat content was, at the same time, increased instead of decreased. Sommerfeld⁵⁹ demonstrated also a higher water content of muscles from athreptic infants. A fat determination was evidently not done. Steinitz⁶⁰ has examined 3 complete athreptic infants and finds an average water content of 81 per cent. about 10 per cent. higher than the figures of Camerer and Söldner⁶¹ on full-term new born infants. This he attributes to the fact that there has occurred a more or less complete disappearance of fat in the athreptic organism. Also Tobler⁶² emphasizes the high water content of muscles of athreptic infants. In a recent article by Klose⁶³ it is found that infants dead directly after an acute weight loss showed a low water content of the skin, while the skin of infants dead from chronic nutritional disturbances without any acute manifestations showed an unusual high water percentage. Schiff and Stransky⁶⁴ studied the water content and water absorption of muscles. They found that muscles from infants dead from acute intoxication could not, after artificial desiccation, reabsorb more than 75 per cent. of the water which they contained before drying. Muscles from athreptic infants, absorbed up to 120 per cent. of the water they originally contained. This seems to indicate that there is a marked difference in the water combining power of the muscle

cells in the acute and chronic nutritional disturbances. Rominger⁶⁵ calls attention to the fact that the so-called hydremic reaction (changes in water content of the blood after subcutaneous saline injection) varies in different types of infants. The curve indicating percentage water in the blood, is rapidly rising and rapidly falling to its previous value in infants suffering from intoxication showing the water need of the tissue. For athreptic infants the curve is very slowly rising and shows a very slow fall, even more slow than that for a normal infant. The author takes this finding as a sign that these infants possess an abundance of water in their organism. At least, there is no water need. He considers this finding as an explanation for the fact that these infants seem to do better on concentrated feedings.

The blood of patients suffering from a variety of other clinical conditions has been examined. These results appear in Table VII.

TABLE VII.

Serum Protein of Infants Suffering From Various Diseases.

Number	AGE	Protein Percentage	DISEASES
1	4 months	5.90	Exudative diathesis.
2	4 "	5.90	Harelip.
3	5 "	6.22	Bronchopneumonia.
5	6 "	6.55	Bronchitis.
6	6 "	4.81	Exudative diathesis.
7	6 "	6.77	Malaria.
9	7 "	7.42	Tetany.
10	7 "	7.42	Tetany.
12	9 "	7.56	Tuberculosis.
13	10 "	7.52	Otitis media.
14	10 "	6.34	Bronchopneumonia; anemia.
15	13 "	8.06	Epidemic meningitis.
16	13 "	7.63	Tuberculosis.
17	13 "	7.20	Congenital syphilis.
18	14 "	8.49	Congenital syphilis.
19	14 "	8.0	Bronchitis.
20	15 "	7.95	Tuberculosis.
21	15 "	5.78	Pneumonia.
22	16 "	5.30	Pneumonia.
23	18 "	8.00	Encephalitis.
24	20 "	8.06	Encephalitis.
25	21 "	7.00	Tuberculosis.
26	2 years	8.12	Rickets.
27	2 "	5.90	Rickets.
28	2 "	7.20	Exudative diathesis.
29	2 "	7.00	Congenital syphilis.
30	3 "	8.36	Acidosis, postoperative.
31	7 "	6.45	Nephritis.
33	1 year	7.52	Bronchopneumonia.

It is seen that the figures do not differ much from those of normal infants.

The high water content of athreptic infants might be considered one of the factors which explains their low immunity.

Experimental work has confirmed the finding of the low immunity of hydrated tissues (Schultz⁶⁷). Weigert's⁶⁸ work emphasized the importance of the water content of the medium for growth of different bacilli; he found further⁶⁹ that pigs fattened on high carbohydrate feeding whose tissues were in a state of hydration, showed an exceptionally low resistance to tuberculosis as compared with normal pigs or those fed on mixtures predominating in fat content. Thomas⁷⁰ and Hornemann⁷¹ corroborated these findings. In a recent work Thomas⁷² has shown that a present infection does not progress to as great extent if a high protein feeding is given.

4. *The Blood Circulation in Infants in Health and Disease (Athrepsia).*

Until recently, observations on the rate of blood flow have been made almost exclusively in the laboratory, since there were no known methods fitted for clinical application.

Two methods have been in general use. One, Ludwig's "Strohmuhr" or various modifications of this; the other, which does not involve any interference with the blood vessels, the plethysmographic method of Brodie. This latter method has long been known but it has found little application to clinical work. Even the application of the plethysmographic method to the arm (Hewlett and von Zwaluwenburg⁷³) has not found any general use.

A method easily adaptable to clinical work is the calorimetric method of Stewart⁷⁴. The principle of this method is; that providing the blood passing from the thorax to the hands or feet is of constant temperature, the rate at which heat is distributed from the hands or feet will be directly proportional to the rate of movement of the blood through these parts. Stewart found that hands, and to a less degree the feet, are good radiators. If the temperature of the environment is not much lower than the temperature of the blood, while this is traversing the part, heat will be lost to the environment until the venous blood has reached the same temperature as the surroundings. When we know how much heat has been given out by the part to the water surrounding it, in a given time, and we know the difference in temperature of the inflowing and outflowing blood, we can easily calculate the blood passed in a unit of time per unit of mass. The formula used for the calculation is $Q = \frac{H}{T - T_1}$, H, being the calories of heat given off to the calorimeter; T, being the temperature of the arterial blood; T₁ being the temperature of the venous blood. We must know the cooling curve and the specific heat of the calorimeter. Stewart worked with a calorimeter especially made for this purpose and found the average blood flow in adults to be 14cc. of blood per hundred grams of hand in one minute.

As the results obtained by this method have never been checked up by results obtained by determining the actual blood flow, some ex-

periments on dogs with Tigerstedt's modification of Ludwig's Strohmur have been done in the physiologic laboratory of Washington University under the direction of Dr. Erlanger. The blood flow was determined on five dogs using the iliac artery on the same side as Stewart's method had been applied, directly before the operation. The results will be seen from Table VIII.

TABLE VIII.

Determination of Blood Flow Using Iliac Artery.

No.	Weight in Gm.	Stewart Method Calc. per 100 cc. Mass in 1 min.	Strohmur Method Calc. per 100 cc. Mass in 1 min.	Blood Pressure in Mm. Hg.
1. Normal dog.....	6,100	15.4 cc.	14.4 cc.	128
2. Normal dog.....	5,200	10.0 cc.	10.4 cc.	120
3. Starved dog (8 days)	4,720	11.16 cc.	10.67 cc.	110
4. Starved dog (6 days)	2,200	5.12 cc.	4.30 cc.	105
5. Starved dog (10 days)	5,200	7.60 cc.	4.30 cc.	90

The figures correspond very well except in one instance.

On applying the method to infants, an ordinary large vacuum food jar was used as a calorimeter. The top was closed by a layer of cork and felt with the necessary openings for the hand, thermometer and stirrer. Since, as far as I know, no studies have ever been made on the blood flow in infancy, the rate in normal infants had to be determined first.

TABLE IX.

Blood Flow of Normal Infants.

Number	A G E	Cc. of blood per 100 Gm. of arm (right) per min.	Number	A G E	Cc. of blood per 100 Gm. of arm (right) per min.
1	$\frac{1}{4}$ month	14	16	7 $\frac{1}{2}$ months	10
2	1 "	15	17	8 "	17
3	2 $\frac{1}{2}$ months	15	18	9 "	19
4	3 "	19	19	9 "	15
5	2 "	15	20	13 "	16
6	3 "	16	21	13 "	19
7	3 "	18	22	16 "	17
8	3 "	20	23	17 "	14
9	3 $\frac{1}{2}$ "	20	24	18 "	20
10	4 "	17	25	19 "	14
11	4 "	17	26	20 "	19
12	4 "	21	27	24 "	16
13	4 "	16	28	2 $\frac{1}{2}$ years	15
14	6 "	20	29	2 $\frac{1}{2}$ "	15
15	6 $\frac{1}{2}$ "	22			

It will be seen from Table IX. that the rate of blood flow in the right arm of the normal infant is fairly constant and varies from 14 to 22 cc. with an average of 17.3 cc. of blood per hundred cc. of arm per minute. Determination made on the foot showed two-thirds of the value for the hand, that is to say, from 11 to 12 cc. per hundred cc. of body.

If we take 17 cc. as the normal flow for infants, we find that the blood circulation in infants is higher than in adults; a fact which I had previously suspected (Uthelm⁷⁶) without having been able to prove.

In Table X. are given the results obtained on the blood flow of athreptic infants. In the case of a number of these infants, several determinations were made on different days and when the infants were in various states of nutrition. These results are recorded. Results are expressed in terms of cc. of blood per 100 grams of arm per minute.

TABLE X.
Blood Flow of Athreptic Infants.

No.	Age, Mo.	Cc.	Cc.	Cc.	Cc.	Cc.	Cc.	Cc.	Cc.
1	1	6	5	5	5	—	—	—	—
2	1	6	6	4	8	12	—	—	—
3	1	3	3	6	—	—	—	—	—
4	1	5	7	—	—	—	—	—	—
5	1	7	7	—	—	—	—	—	—
6	2	6	8	—	—	—	—	—	—
7	2	5	6	6	7	8	—	—	—
8	2	5	—	—	—	—	—	—	—
9	2	7	7	—	—	—	—	—	—
10	2	12	5	5	3	14	—	—	—
11	3	7	—	—	—	—	—	—	—
12	3	5	—	—	—	—	—	—	—
13	3	10	—	—	—	—	—	—	—
14	3	8	—	—	—	—	—	—	—
15	3	9	—	—	—	—	—	—	—
16	3	3	2	1	2	4	3	4	0
17	3	8	3	4	—	—	—	—	—
18	4	3	3	—	—	—	—	—	—
19	4	5	8	15	15	15	15	—	—
20	4	6	—	—	—	—	—	—	—
21	4	9	—	—	—	—	—	—	—
22	4	5	3	2	3	2	4	—	—
23	5	17	22	14	6	3	—	—	—
24	5	4	—	—	—	—	—	—	—
25	5	2	3	4	3	—	—	—	—
26	5	7	5	2	—	—	—	—	—
27	5	13	17	13	18	11	18	—	—
28	5	7	9	3	—	—	—	—	—
29	5	8	—	—	—	—	—	—	—
30	6	5	3	3	—	—	—	—	—
31	6	3	6	—	—	—	—	—	—
32	9	4	3	4	2	4	5	1	3
33	17	11	8	—	—	—	—	—	—
34	18	8	9	—	—	—	—	—	—

Some infants were followed throughout the whole stay in the hospital and showed changes in the rate of blood flow according to their nutritional condition. When the infant gained weight and nutrition improved, the rate of blood flow increased, on the contrary, when the weight dropped and the infant got worse the blood flow decreased constantly until death occurred. This is shown in the curves below, Fig. 4 and 5. Fig. 4 is a curve of a three weeks old infant who was admitted because he would not gain weight. Admission weight was 2500 gms., rate of blood flow on admission 4.5 cc. per 100 cc. arm. The infant did fairly well in the hospital, gained rapidly, the blood flow increased and was at discharge 14 cc., which is not far from normal.

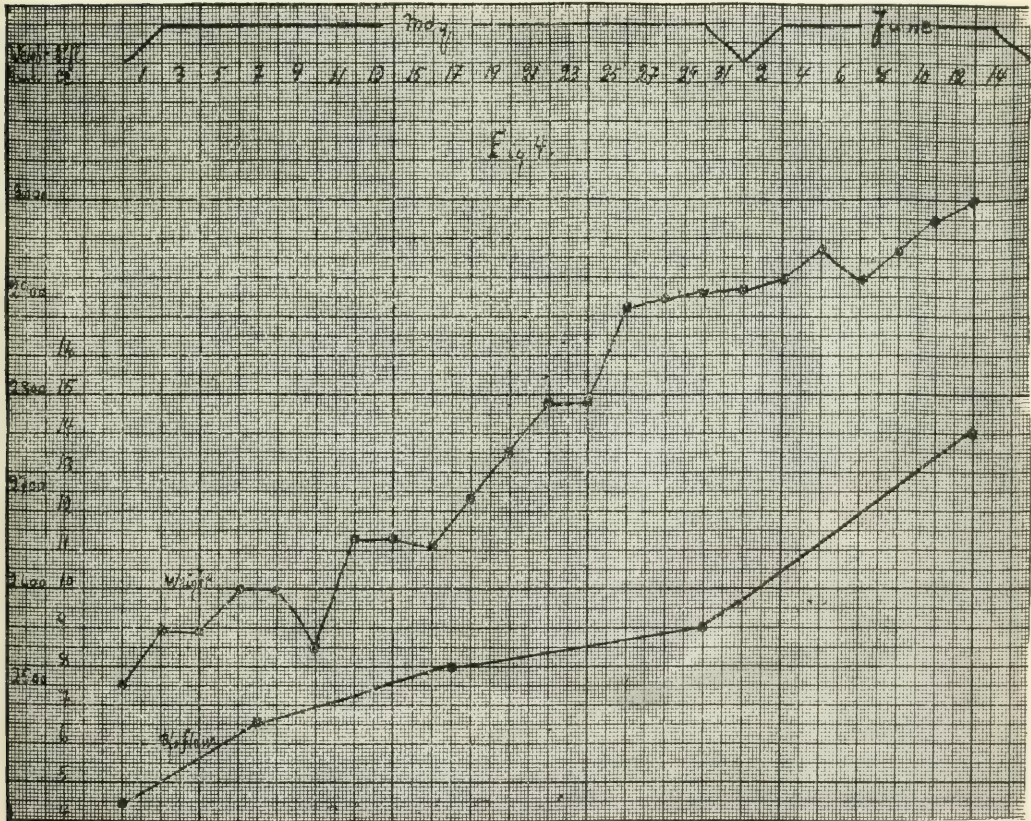


FIG. 4.

Showing increase in rate of blood flow in an infant with increasing weight.

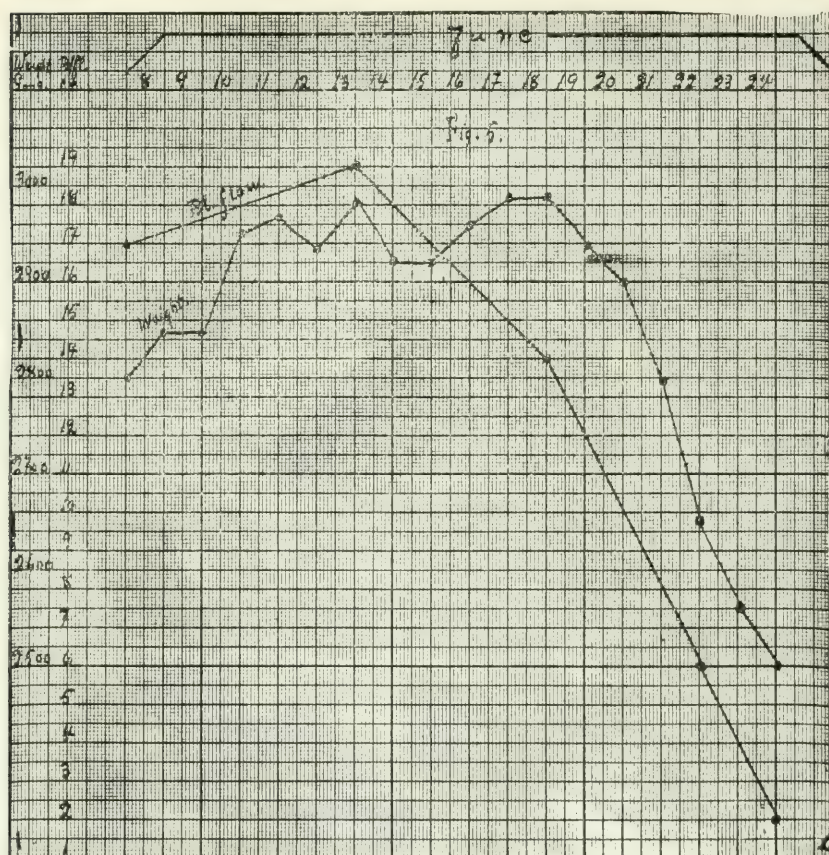


FIG. 5.

Showing fall in rate of blood flow as the weight falls in an athreptic infant.

Fig. 5. is a curve from a very small infant. In spite of the low weight the nutrition was fairly good and the rate of blood flow was good, 17 cc. per 100 cc. arm. The blood flow, taken six days later while weight was going up was even higher, 18 cc. But then the infant started to lose weight rapidly and the movement of the blood became slower until shortly before death it was 2.0 cc. per 100 cc. arm.

The blood flow is greatly increased by injections directly or indirectly into the blood stream. As will be mentioned later, under treatment, intravenous glucose, or glucose acacia solutions have been used a great deal as well as intraperitoneal saline injections. Such injections have nearly always a marked effect on the rate of blood flow, but usually a temporary one only. The increase of blood flow was

noticed three to four hours after an intravenous glucose injection and was about normal, or at least greatly improved for 12 hours. It then dropped down to the previous figure if another injection was not given. The effect of an intraperitoneal saline injection was usually not seen before six to twelve hours afterwards, and did not have such a marked effect as an intravenous injection.

Comparison between the blood flow of athreptic infants, (Table X.) and of infants suffering from various diseases (Table XI) indicate that the low blood flow is a special attribute of athreptic infants and of those suffering from acute diarrhea.

Why do these athreptic infants show this very low rate of blood flow?

The factors which determine the rate of blood flow must be considered. These are four; (1) the condition of the heart, (2) changes in blood viscosity; (3) changes in the total blood volume, (4) influence of the vasomotor system.

As to the heart, electrocardiographic studies made on some of the infants in this series by Dr. McCulloch⁷⁶ have shown that deviations from the normal type of curve may occur. Such changes, are, however, not constantly observed. The blood pressure, as will be seen later, is not usually low. The pulse rate, however, may be slow. There is, at present, not sufficient experimental evidence upon which to base a definite conclusion as to the rôle of the heart in the causation of the low volume flow of the blood. It is certainly necessary to consider other factors.

TABLE XI.

Blood Flow in Infants Suffering From Various Diseases.

No.	Age. Mo.	Diseases	Cc.	Cc.	Cc.	Cc.	Cc.	Cc.	Cc.
1	2	Anemia	27	36	26	28	29	27	17
2	1	Anemia	32	—	—	—	—	—	—
3	7	Anemia	31	—	—	—	—	—	—
4	12	Malnutrition	11	—	—	—	—	—	—
5	6	Malnutrition	10	—	—	—	—	—	—
6	12	Malnutrition	12	—	—	—	—	—	—
7	6	Malnutrition	15	—	—	—	—	—	—
8	9	Malnutrition	15	—	—	—	—	—	—
9	4	Malnutrition	13	—	—	—	—	—	—
10	8	Tuberculosis	9	—	—	—	—	—	—
11	13	Tuberculosis	18	11	11	15	—	—	—
12	22	Tuberculosis	11	—	—	—	—	—	—
13	5	Tuberculosis	11	—	—	—	—	—	—
14	9	Tuberculosis	11	12	—	—	—	—	—
15	12	Tuberculosis	12	—	—	—	—	—	—
16	6	Tuberculosis	21	—	—	—	—	—	—
17	12	Tuberculosis	12	—	—	—	—	—	—
18	21	Tuberculosis	23	—	—	—	—	—	—
19	14	Tuberculosis	13	—	—	—	—	—	—
20	20	Rickets	12	—	—	—	—	—	—
21	24	Congen. Syphilis	15	—	—	—	—	—	—
22	12	Congen. Syphilis	16	—	—	—	—	—	—
23	6	Meningitis	14	13	27	26	25	—	—
24	12	Meningitis	19	14	11	32	—	—	—
25	14	Meningitis	8	—	—	—	—	—	—
26	24	Nephritis	19	—	—	—	—	—	—
27	9	Nephritis	5	8	13	9	—	—	—
28	24	Nephritis	11	—	—	—	—	—	—
29	12	Nephritis	10	—	—	—	—	—	—
30	24	Hypothyroidism	3	—	—	—	—	—	—
31	4	Hypothyroidism	20	—	—	—	—	—	—
32	6	Acute Diarrhea	8	9	8	—	—	—	—
33	9	Acute Diarrhea	2	5	3	3	—	—	—
34	7	Acute Diarrhea	16	—	—	—	—	—	—
35	7	Acute Diarrhea	5	—	—	—	—	—	—
36	8	Acute Diarrhea	3	5	—	—	—	—	—
37	4	Acute Diarrhea	10	8	12	10	10	—	10
38	1	Acute Diarrhea	7	—	—	—	—	—	—
39	2	Acute Diarrhea	6	3	—	—	—	—	—
40	5	Acute Diarrhea	7	8	—	—	—	—	—

As far as the blood viscosity is concerned, this is, as is well known, a function of the protein concentration. As the protein is low in these infants, the change should be on the low side and should tend to increase instead of diminish the circulation.

Passing to the total blood volume, some of the infants examined in this paper showed a diminished blood volume (Marriott¹²), which very well explains the low rate of blood flow. Other cases of athrepsia

however, did not show diminished volume in proportion to the body weight though they showed the same low rate of blood flow. What is the cause in these cases?

The constriction of the peripheral blood vessels must be an important factor.

That such a constriction actually takes place in these emaciated infants seems to be proved in the differences in venous and capillary blood with a higher cell count and hemoglobin content on the capillary side in all cases of athrepsia except one (Table XII.)

TABLE XII.

*Difference Between Venous and Capillary Blood
in Athreptic Infants.*

No.	Age	VENOUS		Hb. per cent.	CAPILLARY		Hb. per cent.
		Erythro- cytes	Leuko- cytes		Erythro- cytes	Leuko- cytes	
1	1½ mos.	98	133
2	4 "	117	123
3	2 "	91	99
4	5 wks.	71	71
5	3 mos.	78	86
6	3 "	100	117
7	1 mo.	100	120
8	4 mos.	108	120
9	3 "	3,416,000	8,800	78	4,704,000	15,600	102
10	3 "	4,312,000	12,400	105	4,880,000	17,600	109
11	4 "	4,880,000	8,400	98	5,184,000	9,000	105
12	2 "	3,296,000	8,000	96	4,056,000	8,600	102
13	2 "	2,160,000	8,000	76	2,360,000	8,600	87
14	3 "	3,080,000	8,000	83	3,152,000	87
15	4 "	2,248,000	8,000	80	2,736,000	14,300	91
16	5 "	5,565,000	17,000	85	6,480,000	12,200	90
17	2 "	2,992,000	19,200	42	3,072,000	24,000	50
18	2 "	2,212,000	18,000	38	2,400,000	20,000	43
19	4 "	4,100,000	18,000	90	5,392,000	22,000	95
20	2 "	1,944,000	13,200	40	2,552,000	14,000	43

Most of the hemoglobin determinations were made by Palmer's method¹⁷, a few were made with the Sahli hemoglobinometer. The Turk counting chamber was used for the cell counts. All determinations were made with the same blood pipette.

Such a difference was not found in normal infants, or infants suffering from various diseases, with the exception of cases of acute diarrhea, one case of tuberculosis, one of nephritis, and one of meningitis.

The next question then arises. Why does this peripheral constriction take place? These infants have to be considered as being in the same physical condition as a starved animal, that is, an organism which

has nothing to waste and works in the most economical way. In order to diminish the loss of heat from the body surface a peripheral constriction takes place. The blood, then, naturally is distributed from the peripheral parts of the body to the internal organs.

TABLE XIII.

Difference Between Venous and Capillary Blood in Normal Infants.

No.	Age	VENOUS		Hb. per cent.	CAPILLARY		Hb. per cent.
		Erythro- cytes	Leuko- cytes		Erythro- cytes	Leuko- cytes	
1	2 mos.	3,976,000	9,000	119	3,912,000	8,000	120
2	9 "	4,560,000	6,400	109	4,136,000	6,500	105
3	14 yrs.	125	125
4	3 mos.	95	90
5	2 yrs.	83	83
6	12 "	100	100
7	2 mos.	83	83
8	4 "	112	113
9	4 "	76	78

TABLE XIV.

Difference Between Venous and Capillary Blood in Different Diseases.

No.	AGE	Diseases	VENOUS		Hb %	CAPILLARY		Hb %
			Erythro- cytes	Leuko- cytes		Erythro- cytes	Leuko- cytes	
1	8 yrs.	Tuberculosis	111	107
2	9 "	Heart Disease	120	105
3	9 "	Heart Disease	123	117
4	2 "	Anemia	57	57
5	12 mos.	Tuberculosis	94	82
6	15 "	Meningitis	78	78
7	9 "	Tuberculosis	80	87
8	4 "	Tuberculosis	91	91
9	2 "	Tuberculosis	85	86
10	6 "	Ac. Diarrhea	83	87
11	13½ "	Meningitis	81	107
12	9 "	Ileocolitis	87	87
13	3 yrs.	Acidosis	97	97
14	1 yr.	Meningitis	114	114
15	2 yrs.	Nephritis	91	100
16	6 mos.	Malnutrition	111	111
17	8 "	Ac. Diarrhea	5,184,000	81	6,352,000	87
18	2 "	Ac. Diarrhea	3,536,000	16,400	65	4,064,000	18,400	70

It is easy to understand how this low rate of blood flow, in some instances from 80 to 90 per cent. less than normal, could be a factor, which, together with the high water content of the blood would still further lower the resistance of these infants.

On account of lack of nourishment and insufficient removal of waste products the body cells will degenerate, the oxidizing power of the body tissue will diminish and the organism will progressively be broken down.

5. *The Blood Pressure in Athreptic Infants.*

A survey of the literature in regard to blood pressure in infancy reveals rather widely varying values for normal infants. The reasons for this are, that the methods employed have been different, examinations have been few, and the selection of material may not have been sufficiently careful.

TABLE XV.

*Blood Pressure of Normal Infants Expressed in
Millimeters of Mercury.*

No.	A G E	Systolic	Diastolic	No.	A G E	Systolic	Diastolic
1	$\frac{1}{2}$ mo.	80	70	17	5 mos.	80	60
2	1 "	85	70	18	6 "	90	80
3	$1\frac{1}{2}$ "	90	70	19	8 "	85	70
4	2 mos.	85	70	20	9 "	85	65
	—	83	65		—	85	60
	—	80	65	21	9 mos.	90	20
5	2 mos.	92	75	22	10 "	97	75
6	3 "	95	80	23	12 "	100	80
	—	95	75	24	12 "	100	80
7	3 mos.	90	75	25	13 "	95	75
8	3 "	95	85	26	13 "	90	60
	—	95	80	27	14 "	98	75
9	3 mos.	95	85	28	15 "	95	60
10	4 "	95	75	29	16 "	100	75
11	4 "	90	75	30	16 "	105	90
12	4 "	95	80	31	19 "	105	80
13	4 "	95	70	32	20 "	98	70
14	4 "	95	75	33	24 "	100	75
15	4 "	95	75	34	24 "	100	80
16	5 "	85	70	35	28 "	95	75
		85	70				

TABLE XVI.

*Blood Pressure of Infant Suffering From Various Diseases
Expressed in Terms of Millimeters of Mercury.*

No.	AGE	DISEASES	Systolic	Diastolic
1	3 mos.	Tetany.	95	90
2	4 "	Malnutrition.	70	50
			75	50
3	4 "	Acute Diarrhea.	100	95
			99	70
			95	77
4	4 "	Adenitis.	95	75
5	5 "	Miliary Tuberculosis.	105	95
6	5 "	Adenitis.	86	65
7	5 "	Diarrhea.	78	65
8	6 "	Pyelitis.	100	85
			100	85
9	6 "	Acute Diarrhea.	105	90
10	6 "	Malnutrition.	65	45
11	7 "	Malnutrition.	95	75
12	7 "	Acute Diarrhea.	100	80
13	8 "	Malnutrition.	85	65
			85	65
14	8 "	Acute Diarrhea.	88	70
			75	55
15	9 "	Tuberculosis.	100	80
			105	80
16	9 "	Acute Diarrhea.	100	80
			100	80
17	10 "	Pneumonia.	94	75
			100	60
18	10 "	Otitis Media	85	60
19	13 "	Epidemic Meningitis.	105	90
20	13 "	Tuberculosis.	88	70
			95	80
			95	60
			90	70
			90	70
21	13 "	Congenital Syphilis.	95	75
22	14 "	Hypothyroidism.	120	80
			120	80
23	14 "	Bronchitis.	105	70
24	14 "	Tuberculosis.	105	90
25	15 "	Tuberculosis.	105	90
			105	90
26	15 "	Meningitis.	95	80
			95	80
27	15 "	Pneumonia.	120	60
28	21 "	Tuberculosis.	90	60
29	24 "	Anemia; rickets.	105	85
			105	85
30	24 "	Tuberculosis.	82	55
31	24 "	Pneumonia.	90	60
32	3 yers.	Acidosis.	115	75

It was found necessary to gather normal material not in order to

make a complete study of the normal blood pressure in infants with its physiologic variations, but in order to be able to compare the results on athreptic infants, with results obtained with the same apparatus, and in the same way, on normal infants. A Tycos sphygmomanometer with a cuff which was made to fit the infant's thigh was used. The auscultatory method was employed. No blood pressures were taken on the arm. The examinations were done between 7 and 9 P.M. when the infants were most quiet. Only those results obtained from infants who were completely quiet have been recorded.

TABLE XVII.
*Blood Pressure of Athreptic Infants Expressed in
Terms of Millimeters of Mercury.*

No.	Age	Weight Gms.	Sys- tolic	Dias- tolic	No.	Age Mo.	Weight Gms.	Sys- tolic	Dias- tolic
1	1	2,625	80	70	15	4	3,500	90	70
			80	70	16	4	2,358	64	35
			80	70				78	60
			85	60				84	55
2	1	2,590	80	70					
3	1	2,500	83	55	17	4	2,860	92	65
4	2	3,625	95	85				85	30
			95	85	18	4	3,000	83	60
			90	73	19	4	3,500	80	60
			95	80					
5	2	3,375	80	65	20	5	3,800	78	65
6	2	2,160	72	50				92	80
7	2	2,430	88	65				92	80
			94	70					
8	2	2,320	75	60	21	6	3,780	90	75
9	2	3,000	90	70				90	65
			80	55				105	95
			83	60					
			85	55	22	6	4,540	90	75
10	3	3,450	93	80	23	7	3,850	82	55
11	3	3,030	98	80	24	7	4,050	95	25
			98	80	25	9	6,075	105	88
12	4	4,225	87	73				105	89
13	4	4,330	100	90				105	85
			95	85				105	85
			95	79				95	70
14	4	2,800	92	75					
			105	85	26	12	6,240	85	70
			100	75	27	17	6,450	85	70
			92	75				90	20

From Tables XV, XVI and XVII it will be seen that the blood pressure of athreptic infants usually does not differ very much from that of normal infants of the same age and from infants suffering from various diseases. In exceptional cases low pressure have been observed (Case 6, 16, 20). It should be mentioned that the results obtained at the thigh are higher than those of other authors who have used the arm for the

determination, evidently due to the fact that the cuff is applied to a larger limb.

It is seen then that the low blood flow is usually not accompanied by a lowering of the blood pressure chiefly on account of the following compensatory factors; (1) a diminution of the blood bed by atrophy of the skin, subcutaneous tissue and musculature; (2) contraction of the small peripheral vessels (3) possible changes in the alimentary blood vessels mentioned by Schiff⁷⁸; these are all factors which tend to make blood pressure high.

After having seen these blood changes which take place in athreptic infants, the question naturally arises "Is it possible to produce experimentally in animals a condition similar to athrepsia, and if we succeed, will the same blood changes take place in this condition as in the infants?" The changes in the total blood volume, which for natural reasons could not be followed closely enough in infants could, in this way, be thoroughly studied. We were especially interested in following the blood changes in very prolonged underfeeding periods. This underfeeding period was produced by putting rabbits on actual starvation, depriving them of water, and after having brought the weight down to an abnormally low level, the weight was kept nearly horizontal for several months, until death occurred.

6. *Changes in Total Blood Volume, Blood Protein, Blood Flow and Hemoglobin During Different Stages of Nutrition (Animal Experiments).*

The serum protein, blood flow and hemoglobin were followed during changes in the nutritional condition in order to see in what relationship these factors stand to the total blood volume of the organism.

For purposes of comparison the blood protein and blood flow in normal animals were first determined (Table XVIII and XIX.)

TABLE XVIII.
Blood Protein in Normal Rabbits.

No.	Weight Gm.	Protein Per cent.	No.	Weight Gm.	Per cent. Protein
1	1,700	6.34	16	3,050	6.65
2	1,600	6.34	17	2,850	8.28
3	2,100	6.12	18	2,330	6.98
4	1,700	5.03	19	2,570	6.98
5	1,950	6.98	20	2,050	6.55
6	1,720	5.90	21	1,920	6.55
7	1,600	6.34	22	2,700	6.12
8	1,820	5.68	23	2,750	6.55
9	1,820	6.12	24	2,500	6.22
10	1,750	6.55	25	2,550	6.12
11	900	6.00	26	2,500	6.44
12	1,720	6.12	27	2,700	6.44
13	1,380	6.22	28	2,150	6.55
14	2,430	6.22	29	2,650	6.55
15	3,120	6.22		Aver.	6.40

TABLE XIX.

Blood Flow of Normal Rabbits Expressed in Terms of Cc. of Blood Per Hundred Cc. of Mass of Hind Leg in One Min.

No.	Weight Gm.	Flow Cc.	No.	Weight Gm.	Flow Cc.
12	1,450	10.64	23	2,250	7.00
13	1,520	8.50	24	2,500	7.58
14	2,330	6.44	25	2,700	7.50
15	3,120	12.80	26	2,500	10.90
16	3,050	8.20	27	2,700	9.80
17	2,850	9.50	28	2,140	9.50
18	2,270	10.60	29	2,750	6.16
19	2,560	12.80	30	1,800	5.80
20	1,860	10.75	31	2,150	8.41
21	1,760	14.00	39	2,400	9.00
22	2,700	10.00		Aver.	8.8

The normal blood protein for rabbits weighing from 1000 to 3000 gm. averages 6.40 per cent.

Normal rabbits weighing from 1500 to 3000 gm. show from 5.8 cc. to 14 cc. with an average of 8.8 cc. of blood flow per hundred cc. of leg per minute.

As far as the total blood volume is concerned, it was of special importance in this work to use a method which required little loss of blood and does no harm to the animal. Such is the dye method of Keith, Rowntree and Geraghty⁷⁹, the principle of which is the introduction directly into the circulation of a nontoxic, slowly absorbable dye which remains in the plasma long enough for thorough mixing, and the determination of its concentration in the plasma, calorimetrically, by comparison with a suitable standard mixture of the dye and serum. Such a dye is vital red.

Those who have made the most careful studies of blood volume in animals, are, perhaps, Dreyer, Ray and Walker⁸⁰ who determined blood volume in rabbits indirectly by bleeding. They found the normal blood volume of a rabbit weighing from 2,000 to 3,000 gm. to be from 4 to 5 per cent. of the body weight.

The results which I have obtained on rabbits appear in Table XX.

TABLE XX.

Blood Volume of Normal Rabbits.

No.	Weight Gm.	Plasma Vol. Cc.	Blood Vol. Cc.	Per cent. of Body Weight	"K"
3	2,100	65	92.8	5.1	1.76
5	1,800	70	100.0	5.5	1.48
6	1,675	60	85.7	5.1	1.64
7	1,520	56	82.6	5.5	1.60
8	1,800	70	100.0	5.4	1.48
10	1,800	50	71.0	4.0	1.64
12	1,820	50	83.3	4.5	1.79
14	2,440	73	108.9	4.5	1.79
15	3,130	80	123.0	4.0	1.73
16	3,050	80	129.0	4.2	1.63
17	2,850	75	115.3	4.04	1.74
18	2,330	72	112.5	4.8	1.59
19	2,570	87	133.8	5.1	1.40
20	2,050	64	104.9	5.1	1.57
21	1,550	64	98.4	5.5	1.48
22	2,700	87	124.7	4.6	1.55
23	2,250	70	116.6	5.2	1.48
24	2,500	73	115.8	4.6	1.59
25	2,450	68	106.2	4.2	1.71
26	2,500	80	123.0	4.9	1.50
27	2,700	75	122.8	4.5	1.58
28	2,150	66	104.7	4.8	1.59
29	2,700	77	122.2	4.4	1.59
Average...					1.60

Dreyer, Ray and Walker⁸⁰ have called special attention to the fact that blood volume is a function of the surface area of the animal, that is to say, the smaller animals have a relatively larger blood volume than heavier animals of the same species and this fact may be expressed by the formula based on Meeh's⁸¹ formula for determining the surface area of the body from its weight. The formula used in warm blooded animal is: $B = \frac{W^{\frac{2}{3}}}{K}$, B being blood in cc.; W being the weight of the animal in gms. and K being a constant to be calculated for each species of animal by experimental determination of the total blood volume and substituting this for B in the equation $K = \frac{W^{\frac{2}{3}}}{B}$, he found K for rabbits to be 1.59. According to my experiments $K = 1.60$. His statement is once more confirmed that the relationship between blood volume and the surface area of the animal is a fairly constant one.

When we now pass to the changes taking place during different stages of nutrition it should be mentioned that various authors have differed considerably in the results obtained. Panum⁸², Voit⁸³, and London⁸⁴, of the earlier authors, feel convinced on the basis of their material that in animals (dogs and rabbits) subjected to complete and exhausting starvation, there is no change in the proportion of blood

to body weight. On the other hand, Bidder and Smith⁸⁵ take an opposite point of view. A. Rasmussen and G. Rasmussen⁸⁶ found in a recent study that the blood volume in woodchucks is lowest when the animals contained a maximum of fat. After dormancy and before food is available the percentage of blood is again high and the most emaciated animals have the highest percentage of blood in proportion to body weight.

My rabbit experiments were done in the following way: After a complete determination of blood volume, blood flow, blood protein, hemoglobin and corpuscular volume the animals were completely fasted, neither food nor water being given until the weight was reduced to the lowest compatible with life. At this stage all the determinations were repeated. An amount of food and water just sufficient to prevent further drop in weight was then given and the determinations repeated at intervals. Most of the rabbits practically maintained their weight for months at the level much below normal. Others gained a little, but were again brought down to the low level and remained there until death occurred.

TABLE XXI. *Results of Experiments on Fasting and Under-Fed Rabbits.*

No.	Weight, Gm.	Date	Days Starva- tion	Days Under- Fiding	Protein Per cent.	Hb. Per Cent.	Corpuscle Vol. Per cent.	Blood Flow, Cc.	Plasma, Cc.	Blood Vol. Cc.	Blood Vol. in per cent. of body weight	Calculated Blood Vol., Cc. K=1.60.	Per cent. dif- ference bet. ac- tual and calcul- ated blood vol.
3	2,100	9/13	0	0	6.12	60	30	—	65	22.8	5.1	100.1	-7.8
4	1,350	9/24	11	0	6.12	60	25	10.6	55	73.3	5.4	76.3	-4.0
	1,520	9/10	0	0	5.03	75	—	1.5	—	—	—	—	—
	1,070	9/18	8	0	7.20	—	—	6.6	—	—	—	—	—
	1,350	9/22	—	4	5.77	—	—	—	—	—	—	—	—
	1,200	10/24	—	34	6.27	70	30	—	48	68.5	5.6	70.61	-3.0
	1,350	11/1	—	46	6.55	—	30	—	58	82.8	6.1	76.3	-7.8
	1,320	11/25	—	65	6.34	—	24	—	55	72.3	5.5	75.21	-4.0
7	1,520	9/10	0	0	6.34	65	32	—	56	82.6	5.5	82.62	0.0
	1,520	9/17	7	0	6.12	70	27	—	52	71.5	5.5	73.30	-2.5
	1,270	10/8	—	21	—	—	—	—	49	64.4	4.9	75.21	-16.7
8	1,320	10/8	0	0	—	60	30	—	70	100.0	5.4	92.48	-7.5
	1,800	9/13	0	0	5.68	—	—	—	50	60.9	5.14	70.0	-14.9
9	1,180	9/19	6	0	6.22	55	35	—	48	73.0	4.02	94.2	-29.0
	1,850	9/14	0	0	6.12	70	—	—	42	57.0	4.03	79.3	-39.0
	1,430	9/24	10	0	—	—	—	—	46	65.7	5.4	70.61	-7.4
	1,200	10/6	—	11	7.63	—	30	—	50	74.6	5.7	74.83	-0.2
	1,310	10/20	—	25	6.77	—	33	—	50	59.5	5.0	67.41	-13.2
	1,120	11/8	—	44	6.22	35	—	—	50	71.0	—	92.5	-30.2
10	1,800	9/11	—	—	6.55	75	30	—	50	60.0	4.8	71.4	-19.0
	1,220	9/20	9	0	7.63	75	20	—	48	—	—	—	—
	1,150	10/7	—	17	6.12	—	—	—	—	—	—	—	—
	1,130	10/21	—	32	7.20	52	—	—	52	67.5	6.0	67.80	-0.4
12	1,160	11/8	—	49	7.52	54	22	—	51	65.3	5.5	69.00	-5.6
	1,820	9/10	—	—	6.12	75	—	—	50	83.3	4.5	93.2	-11.8
14	1,150	9/19	9	0	5.25	75	25.5	—	40	55.9	4.8	68.60	-22.7
	2,440	11/1	0	0	6.72	70	33	6.4	73	108.9	4.5	113.3	-4.0
	1,560	11/18	17	0	7.63	90	36	1.0	55	85.9	5.5	90.10	-4.9
	1,680	11/28	—	10	6.55	70	27	6.76	70	95.8	5.6	88.32	-7.8
	1,775	12/20	—	32	6.22	58	25	—	88	117.3	6.6	91.63	13.3
	1,970	1/9	—	52	6.34	60	26	—	93	125.6	6.3	98.2	21.7
15	3,130	10/4	0	0	6.32	90	35	12.8	80	123.0	4.0	133.7	-8.7
	2,160	11/8	14	0	8.06	90	39	1.0	60	98.3	4.5	104.4	-6.2
	2,650	11/28	—	25	5.47	65	30	7.25	88	125.7	4.7	119.7	4.9
	2,550	12/21	—	47	5.90	60	24	—	110	144.7	5.6	116.7	15.0
	2,370	1/9	—	66	6.34	62	27	—	109	135.6	5.6	111.1	18.0
16	3,050	11/4	—	—	6.65	80	38	8.2	80	129.0	4.2	131.4	-1.8
	1,980	11/17	14	0	8.0	85	—	2.0	60	93.7	4.7	98.5	-5.1
	2,520	11/28	—	10	6.12	62	37	9.24	68	107.4	4.2	115.0	-6.5
	2,250	12/28	—	40	6.55	80	33	—	87	128.3	5.6	108.3	15.6
	2,520	1/11	—	54	6.98	65	33	—	86	128.3	5.1	115.7	9.0

17	2,850	11/1	13	—	8.28	75	35	9.5	75	115.3	4.04	125.60	— 8.8
	1,845	11/14	12	—	10.09	110	38	0.8	57	91.1	4.9	95.47	— 3.0
18	1,800	11/26	0	12	8.49	80	37	—	85	103.1	5.7	92.48	10.0
	2,330	11/6	0	0	6.98	58	36	10.60	72	112.5	4.8	110.8	1.5
	1,500	11/16	10	0	9.0	85	36	—	60	93.7	5.8	85.24	9.0
	1,920	11/29	—	13	6.55	62	23	11.31	80	103.8	5.4	96.56	7.0
	1,980	12/20	—	35	6.34	70	22	—	80	102.5	5.1	98.55	3.9
	1,830	1/10	—	55	6.34	60	26	—	83	112.1	6.1	93.51	16.5
20	2,050	10/30	—	—	6.55	80	39	10.75	64	104.9	5.1	100.9	3.8
	1,230	11/13	14	0	7.20	80	27	3.5	52	71.2	5.7	71.75	0
	1,440	11/26	—	13	7.08	70	32	9.8	67	98.5	6.8	79.70	8.9
	1,380	12/18	—	34	8.06	—	—	—	70	94.5	6.8	77.47	18.0
21	1,350	1/9	—	36	6.98	58	27	7.8	78	106.8	7.8	76.3	28.5
	1,750	10/30	6	—	6.55	70	35	14.0	64	98.4	5.5	90.76	7.7
	1,350	11/6	—	—	8.06	—	23	1.68	58	75.3	5.5	76.3	— 1.0
22	2,700	10/31	—	—	6.12	70	30	10.0	87	124.7	4.6	121.2	2.8
	1,980	11/16	—	—	6.87	80	35	1.2	70	107.6	5.4	98.55	8.3
	2,130	11/29	16	13	5.68	65	29	6.6	68	95.7	4.4	103.50	— 8.9
23	1,620	12/20	—	34	5.68	55	26	—	90	120.0	7.4	86.21	28.1
	2,250	11/6	—	—	6.55	75	40	7.0	70	116.6	5.2	108.3	7.1
	1,560	11/15	9	—	7.42	76	36	1.0	52	81.2	5.2	90.10	— 10.9
	1,720	11/29	—	14	6.77	—	31	11.20	70	101.4	6.7	89.72	11.5
	1,520	12/28	—	43	6.98	53	23	—	85	103.9	7.2	82.62	20.5
24	1,750	1/12	—	58	6.98	53	27	10.7	83	113.7	6.5	90.77	20.3
	2,500	11/4	—	—	7.20	85	37	7.5	73	115.8	4.6	115.2	0
	1,775	11/18	14	—	6.22	85	35	1.7	62	95.3	5.5	96.12	— 0.1
25	2,450	11/4	14	—	6.12	90	36	7.5	68	106.2	4.2	113.6	— 6.5
	1,915	11/18	—	—	8.06	85	31	1.7	52	75.3	4.1	93.0	— 23.9
	2,090	11/29	—	11	6.34	70	28	13.33	64	88.8	4.3	103.20	— 16.2
	1,875	12/18	—	30	7.63	—	33	—	71	105.9	5.6	94.9	10.3
26	2,020	1/9	—	52	7.20	70	34	8.0	70	106.0	5.2	99.87	5.6
	2,500	11/1	—	30	6.44	70	35	10.9	80	123.0	4.9	115.10	6.4
	1,620	11/15	14	—	7.63	—	30	0.8	65	92.8	5.7	86.21	7.1
	1,890	11/26	—	11	6.00	—	25	11.89	66	88.0	4.1	95.54	— 8.5
	1,830	12/21	—	35	—	60	27	—	75	102.2	5.6	93.51	8.9
27	1,730	1/10	—	55	6.34	65	33	—	75	102.2	6.1	90.05	15.7
	2,700	11/1	—	—	6.44	70	39	9.8	72	107.4	4.5	121.22	1.3
	1,800	11/18	17	—	8.28	80	35	1.5	75	122.8	5.3	92.5	4.1
	1,970	11/28	—	10	6.98	63	27	3.16	63	96.5	5.0	98.22	0.4
	1,800	12/18	—	30	7.33	—	24	—	71	98.6	5.2	92.48	10.3
	1,900	12/29	—	41	6.34	55	23	8.32	78	103.2	—	—	—
	2,220	1/10	—	53	7.20	65	27	—	92	126.0	5.7	106.30	8.1
28	2,150	11/2	—	—	6.55	75	37	9.5	66	104.7	4.8	106.5	— 1.7
	1,320	11/16	14	—	6.77	75	37	1.3	40	63.4	4.8	75.21	— 18.6

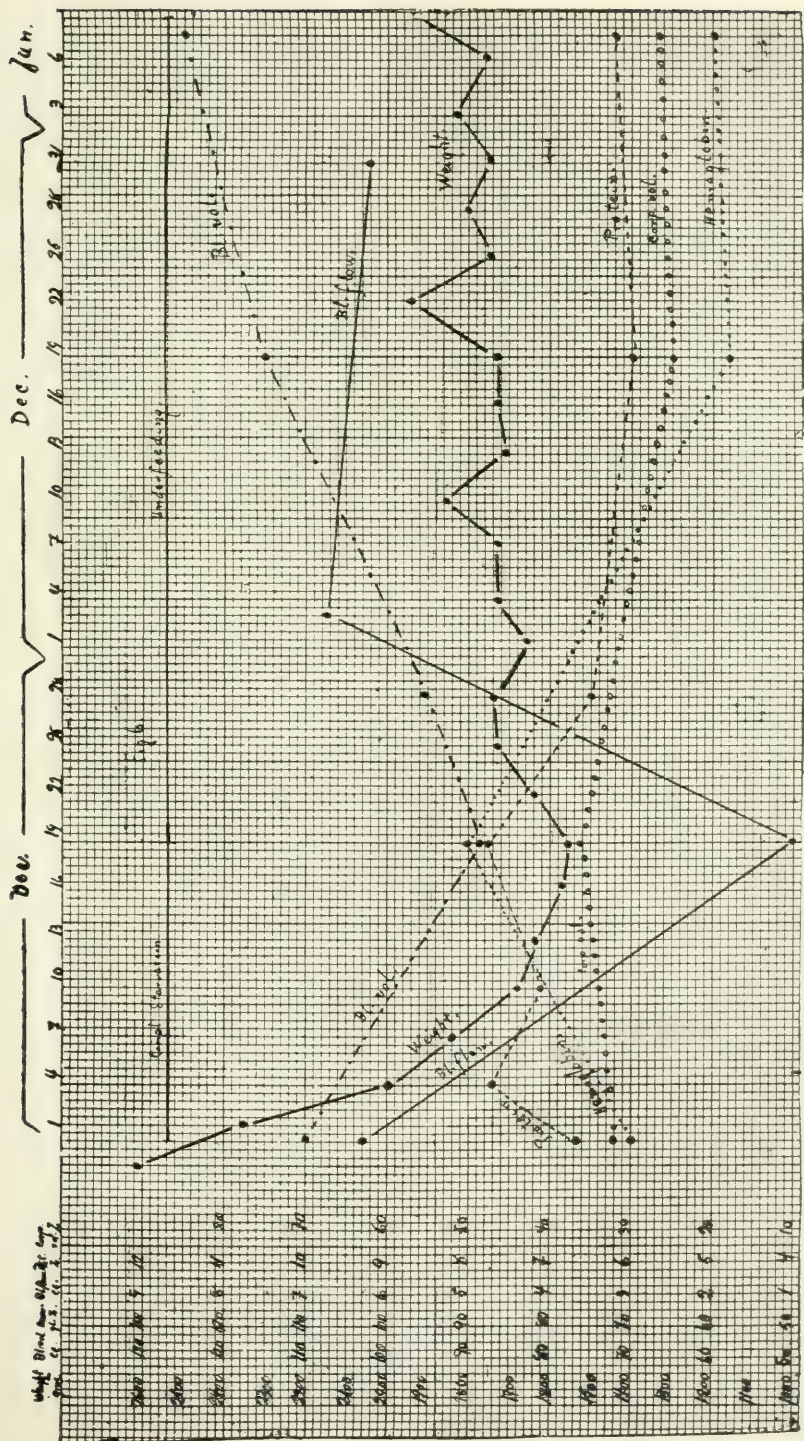
In referring to Table XXI. it will be seen that twenty-one rabbits were examined in the way described. Of these, six died of complete starvation and fifteen were followed in the period of prolonged under-feeding. According to the formula $B = \frac{W^{\frac{2}{3}}}{K}$, K being calculated from own measurements on normal rabbits, a theoretical blood volume has been determined and the present difference between the actual and theoretical blood volume put in one column.

It will be seen that most of the rabbits in the second determination, that is, the day after the longest complete starvation before food and water had been given, showed a negative difference between the actual and theoretical blood volume. They have, at this stage, a smaller volume than they should have according to the surface area. The differences are, however, sometimes very small.

That it is mostly water which disappears from the blood in this period of complete starvation can be seen from the figure for protein, hemoglobin and corpuscular volume, which rise during this period.

The blood flow decreases from the normal 8 or 10 cc. to as low as 1 cc. after the longest periods of starvation. This is, of course, partly due to the diminished volume, but, as mentioned before, since the difference between the actual and theoretical value is very small, we must think of other factors. The blood flow determined in these experiments is the peripheral flow, the rate through the rabbit's hind legs. We know from experience, that nature is always the most economical worker. With lack of food the animals keep quiet and by contraction of the peripheral arterioles heat may be conserved and the blood distributed to those organs whose functional activity is essential to life. In this way the low rate of blood flow found is explained.

As soon as fluid and food were given the rabbits even when no more than enough to prevent further loss of weight, the blood volume in most cases was rapidly restored, so that in the third or the fourth determination there was a positive difference between actual and calculated blood volume. The protein concentration became normal and blood flow increased. Figure 6 (rabbit 14) shows graphically the changes here mentioned.



Showing bloodvolume, serumprotein, hemoglobin and corpuscular volume during complete starvation and during prolonged underfeeding period in a rabbit.

Four of these rabbits did not reach a positive difference between actual and calculated blood volume during under feeding (Nos. 4, 7, 9 and 10, Table XXI). Of these, however, two (Nos. 9 and 10) showed a negative difference in the first control observations, and one (No. 7) showed no difference whatever, and on one (No. 4) the normal result was not taken. It is of interest to note that all these four rabbits failed to gain in weight, even though plenty of food was given, and two of them (Nos. 9 and 10) developed skin infections. The skin infection did not affect any of the others, though all were kept in the same room. It is, perhaps, only fair to attribute the poor condition of these four rabbits to the low blood volume.

It is furthermore to be noted that these last four rabbits were all young animals with a low weight. These were the only very young rabbits which it was possible to carry through the underfeeding period. All others of the same age and same weight died very rapidly. The important question of age enters here. These rabbits were actually in an athreptic stage if we can use the expression applied to infants. They had all the signs from which we diagnose this condition. They were under-nourished, they would not gain in spite of food given, the temperature was subnormal and skin infection appeared towards the end of life. They were all growing animals and perhaps this condition developed because the reserve power necessary for growth was insufficient. During their prolonged underfeeding period, some changes must have taken place in these young cells so that a further development with regeneration of the blood volume did not occur even when an excess of food was given.

These changes which occur in the organism of the athreptic infant—the diminished flow of blood in the peripheral part of the body, the close relationship between the nutritional condition of the infant and the degree of impairment of the circulation, the diminished total blood volume,—are all factors which would naturally tend to lower the oxidizing power of the tissues and render the metabolism in such an organism incomplete. An attempt was made, therefore, to investigate the intermediate metabolism of these infants.

7. *Oxidative Function of the Body in Athrepsia.*

In order to obtain an idea of the oxidizing power of the body the ability of these infants to oxidize benzol to phenol was measured. According to Nencki and Giacosa⁸⁷, benzol is oxidized in the body of normal individuals to phenol, pyrocatechin and hydropinone compounds, which are excreted in the urine, usually in combination with sulphuric acid. Benzol is also oxidized to phenol outside of the body, providing conditions are such that nascent oxygen is present (Leeds⁸⁸, Hoppe-Seyler⁸⁹, Nencki and Sieber⁹⁰, Radziszewski⁹¹). Nencki and Sieber⁹² have stated that normal adults tested at different periods excreted constant amounts of phenol after the administration of a definite amount of benzol. They showed that in diseases such as leukemia and pseudo hypertrophic muscular dystrophy the excretion of phenol

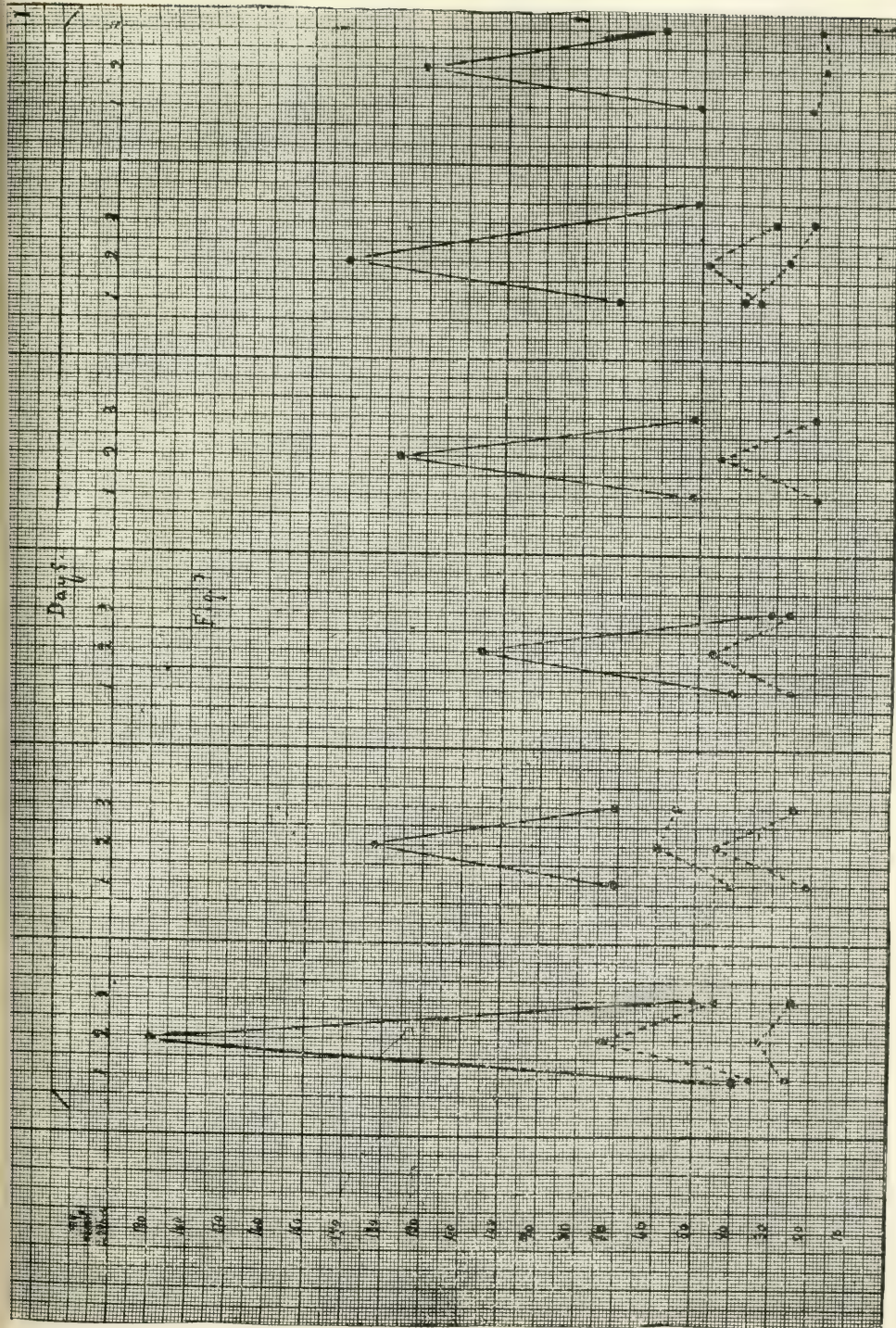


FIG. 7.

Showing excretion of phenols in the urines of infants following the administration of 0.5 gm. benzol by mouth. Each line represents an experiment on one infant. The first dot fore period; the second dot period following benzol administration; third dot after period. Solid lines represent results from normal infants; the broken ones those from athreptic infants.

was somewhat diminished. Simanowski and Schaumoff⁹³ found a diminished excretion of phenol in alcohol intoxication. The same authors also determined in animal experiments that an insufficient oxygen intake, produced by mechanical pressure on the trachea, until dyspnea was produced led to a decreased oxidation of benzol to one-third of the normal amount. In 1902 Freund⁹⁴ administered benzol to two athreptic infants and found less phenol excreted in the urine than in the case of normal infants.

My own observations were made on fifteen infants. Six of the infants were in fairly good nutritional condition, the remaining nine were all athreptic. Each infant was examined for a period of seventy-two hours. The total phenol was determined by Folin's⁹⁵ method. During the first twenty-four hours the normal phenol output in the urine was determined. At the beginning of the second twenty-four hour period 0.5 gm. benzol were administered by mouth. During the third twenty-four hour period no benzol was administered. The experiment was discontinued in every instance in which vomiting occurred. The results appear in Table XXII. and are shown graphically in Figure 7.

It will be seen from Table XXII that normal and athreptic infants react very differently to the administration of benzol. The increase in phenol output after administration of benzol to the normal infants was from 60 to 155 mg. whereas in the athreptic infants it did not exceed 36 mg. in the twenty-four hours. The objection which may be made is that the low phenol excretion is due simply to the poor absorption of the benzol given by mouth. In order to determine if this were the case, the stools from both normal and athreptic infants have been examined, after the administration of benzol by mouth and in no instance was any benzol found (method of Allen⁹⁶). It seems, therefore that one is justified in stating that the tissues of infants suffering from an advanced chronic nutritional disorder are incapable of oxidizing benzol to phenol.

8. *Caloric-Nitrogen and Carbon-Nitrogen Ratios.*

The next step was to determine whether there was any evidence that such decreased oxidation resulted in metabolic disturbances. It was thought that by examining the energy factors of the urine we would gain an insight into the metabolism of these infants, especially by determining the energy factors in relation to the nitrogen content, or, in other words, what has generally been referred to as the carbon-nitrogen and the caloric-nitrogen ratio which will be referred to hereafter as C-N and Cal-N respectively. The C-N ratio has been studied more than the Cal-N ratio, but as the two are approximately proportional in different urines, they are of equal significance. Two important constituents of normal urine, urea and ammonia, give carbon nitrogen ratios of 0.43 and 0 respectively, and tend to keep the ratio in the total urine low. Uric acid, creatinin, amino acids and other organic compounds in normal urine raise the ratios. As the result of a disordered metabolism there were conceivably therefore present in

the urine, products which contained considerable amounts of carbon, and relatively small amounts of nitrogen, if any. The most important of these substances are perhaps the organic acids, sugar, amino acids and certain protein decomposition products, such as described by Bonzynski and Gottlieb⁵⁷ by Cloetta⁵⁸ and later by Pregl⁵⁹ under the name of "oxyproteic acid".

TABLE XXII.

Phenol Excretion After 0.5 Gm. Benzol Intake on Second Day.

No.	Diagnosis	Weight	Age Mos.	Mg. Total Phenol Excretion in 24 hours			Mg. Free Phenol Excreted in 24 hours.		
				1st. Day	2nd. Day	3rd. Day	1st. Day	2nd. Day	3rd. Day
1	Athrepsia	2,050	2	28.7	33.5	25	11.9	14.3	12
2	Athrepsia	4,200	2½	38.7	74.3	47	31.8	59.2	35.1
3	Athrepsia	3,870	8	40.85	61.09	55.7	17.7	28.7	43.2
4	Athrepsia	2,800	2	21.3	45.9	25.07	9.9	22.2	14.8
5	Athrepsia	2,070	2½	27.2	47.9	30	15.2	19.	14.2
6	Athrepsia	2,800	2½	21.	46.8	22	13.6	30.4	15
7	Athrepsia	5,550	18	35.65	49	22	21.9	23	20
8	Athrepsia	3,100	6	38.2	29.4	21.3	20.4	20.3	13
9	Athrepsia	2,500	1½	21.77	17.8	21.5	13	10.3	14.5
10	Normal baby	7,900	7	36	191.2	50	28	76	25
11	Normal baby	4,850	3½	73.5	132.4	71.3	42.1	43.5	35.6
12	Normal baby	4,850	3½	40.4	105.8	30	26.7	105.8	25
13	Tuberculosis (Nutri. good)	6,200	10	54.3	129.7	54.8	24	51.6	18.2
14	Convalesc. from Ac. diarrhea	5,850	10	72	140.1	52.4	72	108.7	47.6
15	Recovered Athrepsia	4,250	8	51	123.9	59.9	33.1	83.2	51.3

According to earlier researches, the two ratios under discussion seem to be fairly constant in the urines of normal adults. Benedict and Miller¹⁰⁰ reported an average C-N ratio of 0.73 and Cal-N of 8.09 as a result of fifty-eight metabolism studies. The variations among the different individuals was small, 0.67 to 0.89 and 7.3 to 8.94 respectively. Magnus-Alsleben¹⁰¹ states that C-N ratio varies in normal individuals between 0.7 and 1.0 and furthermore that the variations do not depend on the diet when this is kept within ordinary limits. Tangl¹⁰² found a slight increase following a meal extraordinarily rich in carbohydrate. The ratios, however, were no higher than those obtained by Magnus-Alsleben. Benedict and Miller¹⁰⁰ were unable to find a change in the ratio which could be ascribed to variations in diet. An increase in the ratio, however, has been found during fasting (Benedict¹⁰³, Benedict and Diefendorf¹⁰⁴) in mountain sickness

(Loewy¹⁰⁵) and following severe muscular exercise (Magnus-Alsleben¹⁰¹) (Higgins and Benedict¹⁰⁶).

As far as infants are concerned the first examination of the C-N was done by Rubner and Heubner¹⁰⁷ on one normal breast fed infant. They found a high C-N ratio, 1.26. Van Oordt¹⁰⁸ working with two breast fed infants, one of which was receiving an extra carbohydrate feeding and Langstein and Steinitz¹⁰⁹ working with several breast-fed infants found also a high C-N ratio in the urine. They did not determine the Cal-N ratio. They attribute the high ratios to the presence in the urine of "extractive substances" from the breast milk. These findings are at variance with those described by other authors working with adults who found little or no effect of the diet on the ratios. If these figures were correct one would have to assume a different behavior of the infant's organisms.

In my own experiments the caloric value of the urine was determined in the Riche adiabatic bomb calorimeter. The urine was prepared for combustion according to the method of Higgins and Benedict¹⁰⁶. The urine was collected every hour without added preservative and immediately placed on ice. It was dried in a current of air at room temperature after the addition of an accurately weighed portion of salicylic acid and then burned in the bomb. It has been shown by Higgins and Benedict that the loss of nitrogen by this method of drying is less than 2 per cent. After the urine was burned in the bomb, the carbon dioxide formed during combustion, was determined according to the method of Fries¹¹⁰ by passing the gas through freshly prepared soda lime. The absorbed carbon dioxide was determined gravimetrically. The remaining carbon dioxide in the bomb was thoroughly washed out by the passage of 9 liters of carbon dioxide free air. In calculating the results in the combustion, due allowance was made for the heat of combustion of the salicylic acid, and for the heat developed in the calorimeter by the action of the electric stirrer.

Total nitrogen in the urines was determined on fresh specimens by the Kjeldahl method. Each specimen of urine was tested for sugar (Benedict method) and for albumin (heat and acetic acid.) The results appear in Table XXIII and XXIV.

In Table XXIII. are shown the results of experiments in which only the caloric nitrogen ratio was determined and not the carbon nitrogen. As will be seen from both tables (XXIII. and XXIV.) the caloric nitrogen ratio for a normal baby, whether breast fed or not, varies from 5.7 to 9.8 and the carbon nitrogen ratio from 0.64 to 0.77. The infants suffering from acute diarrhea showed somewhat higher ratios and those suffering from athrepsia unusually high ones, with one exception (No. 14 Table XXIV).

Infants who were examined over a long period of time were found to show changes in the ratios corresponding to their nutritional condition. For example, infant No. 10, Table XXIII. was admitted in very poor condition, weight 3,080 gm. age 3 months. The C-N ratio was at that time very high, up to 21. The baby was fed on breast milk and started very soon to improve. After five weeks the infant had gained

700 gms. and the Cal-N ratio was quite normal. This is depicted graphically in Fig. 8.

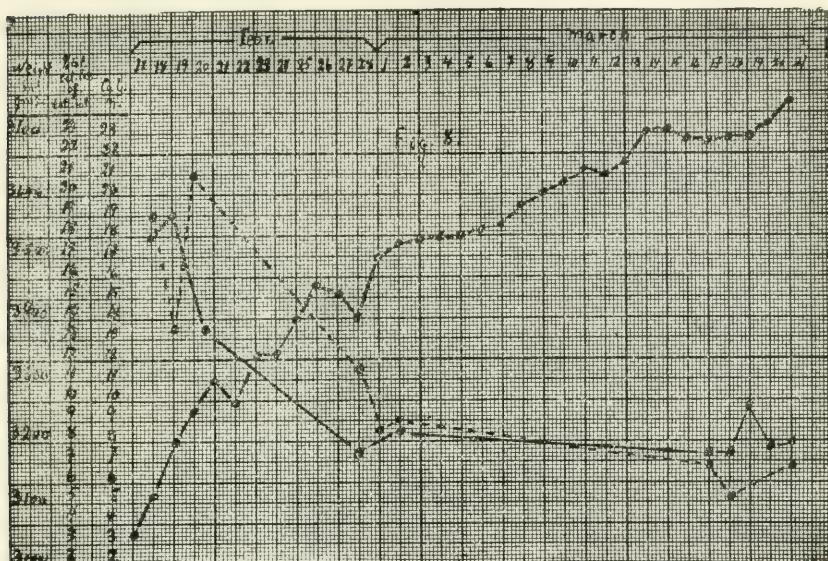


FIG. 8.

This chart shows relationship between the nutritional condition and calorie-nitrogen ratio and utilization of ingested food.

The high ratios obtained in the athreptic infants would indicate that the urine contained compounds of a higher combustion value than under normal conditions. The next step was an attempt to determine the nature of these organic compounds.

The normal urinary constituents which would raise this ratio are creatine, uric acid and the amino acids if present in excessive amounts. Determinations of each of these substances in the urines of the athreptic infants were made.

9. Creatinin, Uric Acid, Amino-Acids of the Urine.

For the determination of creatinin, uric acid and the amino acids, twenty-four hour specimens of urine were used. The urine bottles were collected every hour during the day and every two hours during the night. The urine was preserved with toluol and examined immediately at the end of twenty-four hours. Creatinin was determined by the method of Folin¹¹¹, uric acid by the microchemical calorimetric method of Folin and MacCallum¹¹² as modified by Benedict and Hitch-

TABLE XXIII.
Caloric-Nitrogen Ratio of Infants' Urine.

No.	Diagnosis	Date	Age Mos.	Weight	Feeding	Sugar	Albumin	Cc. Urine in 24 hrs.	Gm. Total N. in 24 hours	Large Calories in 24 hours	Cal-N
1	Normal baby	3/10	1	3,500	Br. Fed	—	—	50	0.132	0.92	7.0
2	Normal baby	2/28	1	4,520	Br. Fed	—	—	280	0.537	4.03	7.5
3	Normal baby	2/13	18	9,300	W.M. Mixt.	—	—	470	3.12	29.95	9.6
4	Normal baby	2/11	13	10,000	W.M. Mixt.	—	—	640	2.22	17.25	7.7
5	Normal baby	2/13	13	10,000	W.M. Mixt.	—	—	500	5.74	32.96	5.7
6	Normal baby	1/7	4	6,300	W.M. Mixt.	—	—	320	0.947	8.99	9.5
7	Pyloric Stenosis	1/24	5	2,900	W.L.M.	—	—	90	1.000	6.12	6.2
	Ac. Diarrhea	1/9	9	4,300	W.L.M.	—	+	425	1.258	13.30	10.6
		1/8	9	4,380	W.L.M.	—	+	125	1.00	11.30	11.3
		1/13	9	4,100	W.L.M.	—	+	110	0.792	9.18	11.6
8	Ac. Diarrhea	1/26	9	4,100	W.L.M.	—	+	638	2.679	35.60	13.3
9	Malnutrition	1/31	2	4,900	W.L.M.	—	—	300	0.492	5.34	10.9
		2/18	2	3,250	W.L.M.	—	—	195	0.702	7.56	10.8
		2/19	2	3,250	W.L.M.	—	—	200	0.512	3.84	7.5
10	Athrepsia	2/18	3	3,180	Br. fed	—	—	230	0.763	14.6	19.2
		2/19	3	3,200	Br. fed	—	—	200	0.616	8.17	13.2
		2/20	3	3,250	Br. fed	—	—	430	0.43	9.04	21.0
		2/28	3	3,400	Br. fed	—	—	500	0.520	5.99	11.5
		3/1	3	3,450	Br. fed	—	—	620	0.768	6.19	8.5
		3/2	3	3,500	Br. fed	—	—	580	0.881	7.52	8.5
		3/17	4	3,680	Br. fed	—	—	346	1.204	8.64	7.2
		3/18	4	3,680	Br. fed	—	—	425	0.884	4.60	5.2
		3/19	4	3,680	Br. fed	—	—	300	0.60	3.60	6.0
		3/21	4	3,780	Br. fed	—	—	460	1.177	7.82	6.6
11	Athrepsia	2/7	1½	2,530	W.L.M.	—	—	300	0.396	5.64	14.4
12	Athrepsia	1/15	3½	3,500	Br. fed	—	—	410	0.541	8.12	15.0
13	Athrepsia	3/29	2	2,680	W.L.M.	—	—	244	0.517	6.20	11.9
14	Athrepsia	4/20	2	2,850	W.L.M.	—	—	332	0.575	6.75	11.7
		4/21	2	2,900	W.L.M.	—	—	279	0.658	7.23	10.9
		4/22	2	2,950	W.L.M.	—	—	230	0.34	5.04	14.8

TABLE XXIV.
Calorie-Carbon-Nitrogen Ratio of Infants' Urine.

No.	Diagnosis	Date	Age Mos.	Weight	Feeding	Sugar	Albu- min	Cc. urine in 24 hr.	Gm. total N. in 24 hrs.	Large Calories in 24 hrs.	Total carbon in 24 hrs.	CalN	CN
1	Normal baby	2/25	2	3,690	Br. fed	—	—	260	0.70	6.91	0.54	9.8	0.77
2	Normal baby	2/28	2	4,000	Br. fed	—	—	280	0.49	4.45	0.35	9.0	0.72
3	Normal baby	2/12	13	10,100	Infant Diet	—	—	580	3.06	24.82	1.96	8.1	0.64
4	Normal baby	2/12	18	9,300	Infant Diet	—	—	230	1.01	8.48	0.65	8.4	0.65
5	Normal baby	2/25	1	4,520	Br. fed	—	—	190	0.47	4.56	0.34	9.7	0.74
	Normal baby	5/2	—	—	W.M.Mixt.	—	—	600	2.90	19.77	1.74	6.8	0.64
		5/2	—	—	W.M.Mixt.	—	—	564	3.61	22.89	2.24	6.3	0.62
		4/2	—	—	W.M.Mixt.	—	—	420	2.68	25.65	2.28	9.6	0.85
6	Parenteralinfect	7/7	16	12,000	W.M.Mixt.	—	—	440	7.48	30.32	6.16	4.9	0.53
7	Exudative												
	Diathesis	3/10	7	4,500	W.M.Mixt.	—	—	280	1.23	9.46	0.74	7.6	0.6
8	Tb. meningitis	2/10	18	9,600	W.M.Mixt.	—	—	170	1.7	17.0	1.68	10.0	0.99
		2/11	18	9,600	W.M.Mixt.	—	—	200	0.64	7.74	0.68	12.1	1.07
9	Ac. Diarrhea	1/8	9	4,700	W.M.Mixt.	—	—	80	1.28	10.56	1.36	8.25	1.06
10	Malnutrition	2/20	3	3,300	W.L.M.	—	—	180	0.55	6.84	0.57	12.4	1.03
		3/8	3	3,300	W.L.M.	—	—	260	0.93	10.71	0.81	11.5	0.87
11	Athrepsia	1/24	3	3,200	Br. fed	—	—	130	0.26	6.34	0.52	24.4	2.00
		1/28	3	3,250	Br. fed	—	—	680	0.82	10.2	0.99	12.4	1.22
		2/1	3	3,300	Br. fed	—	—	420	0.47	4.99	0.79	10.6	1.7
		2/10	3	3,450	Br. fed	—	—	350	0.52	6.47	0.75	12.4	1.45
12	Athrepsia	3/24	3	1,930	Br. fed	—	+	180	0.31	6.61	0.61	21.3	2.0
		3/25	3	1,970	Br. fed	—	+	140	0.18	3.19	0.42	17.7	2.3
		3/26	3	1,980	Br. fed	—	+	290	0.46	6.35	0.69	13.7	1.5
		3/27	3	2,000	Br. fed	—	+	300	0.60	7.20	0.87	12.0	1.48
13	Athrepsia	4/19	2	2,620	W.L.M.	—	—	220	0.38	6.14	0.54	16.1	1.42
14	Athrepsia	4/26	1	2,600	W.L.M.	—	+	40	0.39	4.65	0.36	11.9	0.93

TABLE XXV.
Creatinin Output in 24 hours.

No.	Diagnosis	Date	Age Mos.	Weight	Feeding	Mg. Total Creatinin	Mg. Creatinin per Kg. body wght.
1	Normal baby	9/2/20	7	7,900	W.M.Mixt.	72.0	9.1
		9/8/20	7	7,900	W.M.Mixt.	72.0	9.1
2	Normal baby	12/9/20	20	10,800	Inf. Feed	115.5	10.5
3	Tuberculosis	9/3/20	10	6,200	Inf. Feed	50.0	8.06
		9/4/20	10	6,200	Inf. Feed	47.7	7.7
		9/5/20	10	6,200	Inf. Feed	25.5	4.03
4	Pneumonia	12/15/20	18	13,888	Inf. Feed	58.0	4.10
5	Exudative						
	Diathesis	3/10/21	7	4,500	W.M.Mixt.	28.0	6.20
6	Cretinism	9/14/20	6	3,100	W.L.M.	56.0	18.6
		9/15/20	6	3,100	W.L.M.	39.9	12.8
		9/16/20	6	3,100	W.L.M.	29.3	9.4
7	Malnutrition	12/24/20	13	6,000	W.L.M.	25.16	4.1
8	Ac. Diarrhea	12/14/20	3½	5,200	Prot. M.	38.10	7.3
9	Ac. Diarrhea	9/27/20	10	5,850	W.L.M.	79.8	13.6
		9/28/20	10	5,850	W.L.M.	53.2	9.6
		9/29/20	10	5,850	W.L.M.	34.8	5.9
10	Athrepsia	12/10/20	2	2,050	Br. M.	14.2	6.9
11	Athrepsia	9/14/20	5	3,200	Br. M.	24.0	7.5
12	Athrepsia	9/8/20	2½	2,700	W.L.M.	11.84	4.3
		9/9/20	2½	2,680	W.L.M.	7.40	2.7
		9/15/20	2½	2,600	W.L.M.	10.0	3.8
		9/17/20	2½	2,500	W.L.M.	16.12	6.4
13	Athrepsia	9/20/20	8	3,870	W.L.M.	34.00	8.8
		9/23/20	8	3,800	W.L.M.	41.00	10.7
14	Athrepsia	9/23/20	10	5,300	W.L.M.	59.55	9.5
		9/24/20	10	6,280	W.L.M.	49.20	7.8
		9/25/20	10	6,220	W.L.M.	45.00	7.2
		10/27/20	10	5,200	W.L.M.	55.50	10.6
		10/28/20	10	5,150	W.L.M.	47.60	9.2
		3/18/21	10	3,680	W.L.M.	21.0	5.7
		3/19/20	10	3,680	W.L.M.	18.6	5.05
		3/20/20	10	3,700	W.L.M.	18.6	5.02
		3/21/20	10	3,780	W.L.M.	25.2	6.8
15	Athrepsia	3/10/21	1½	2,420	W.L.M.	16.0	6.6
		3/11/21	1½	2,488	W.L.M.	14.8	6.0
		3/12/21	1½	2,500	W.L.M.	29.3	11.7
		3/13/21	1½	2,540	W.L.M.	20.1	7.9
		3/14/21	1½	2,560	W.L.M.	13.6	5.3
16	Athrepsia	3/8/21	3	3,250	W.L.M.	41.6	12.8
17	Athrepsia	3/12/21	3	3,630	Br. M.	18.18	5.0
18	Athrepsia	3/21/21	5½	4,390	Br. M.	13.0	2.9
		4/4/21	5½	4,390	Br. M.	13.44	3.06
19	Athrepsia	3/24/21	3	1,930	Br. M.	10.8	5.5
		3/25/21	3	1,920	Br. M.	7.3	3.7
		3/26/21	3	1,980	Br. M.	7.2	3.6
		3/27/21	3	2,000	Br. M.	12.3	6.1
		4/4/21	3	2,290	Br. M.	24.0	2.8
		4/5/21	3	2,110	Br. M.	8.3	3.9
		4/6/21	3	2,140	Br. M.	9.6	4.4

TABLE XXVI.

Uric Acid Output in 24 Hours.

No.	Diagnosis	Date	Age Mos.	Weight	Feeding	Mg. total of Uric Acid	Mg. Uric Acid per Kg. body wght.
1	Normal baby	9/2/20	7	7,900	W.M.Mixt.	127.4	16.0
		9/8/20	7	7,900	W.M.Mixt.	240.0	30.0
2	Normal baby	1/2/21	4	6,300	W.M.Mixt.	80.7	11.2
3	Normal baby	12/7/20	9	7,100	W.L.M.	138.0	19.4
4	Normal baby	10/3/20	4½	4,550	W.L.M.	131.0	27.0
		10/4/20	4½	4,818	W.L.M.	159.0	33.0
5	Pneumonia	12/15/20	18	13,888	Inf. Diet	125.0	9.0
6	Tuberculosis	9/3/20	10	6,200	Inf. Diet	76.0	12.2
		9/4/20	10	6,200	Inf. Diet	86.0	13.8
		9/5/20	10	6,200	Inf. Diet	165.0	26.6
7	Cretinism	9/14/20	6	3,100	W.L.M.	95.0	30.6
		9/15/20	6	3,100	W.L.M.	71.3	23.0
		9/16/20	6	3,100	W.L.M.	37.0	11.9
8	Ileocolitis	9/20/20	9	6,200	W.L.M.	82.6	13.3
		10/1/20	9	6,000	W.L.M.	9.0	1.5
		10/2/20	9	5,850	W.L.M.	10.4	1.7
9	Ileocolitis	11/30/20	9	5,600	W.L.M.	77.0	14.1
10	Ac. Diarrhea	9/28/20	10	5,850	W.L.M.	113.7	19.2
		9/29/20	10	5,850	W.L.M.	60.0	10.2
11	Ac. Diarrhea	12/14/20	3½	5,200	Prot. M.	410.0	78.8
12	Ac. Diarrhea	12/15/20	7	5,050	W.L.M.	150.0	29.7
13	Ac. Diarrhea	1/8/21	9	4,300	W.L.M.	159.37	40.0
14	Ac. Diarrhea	3/10/21	7	4,500	W.M.Mixt.	56.0	12.4
15	Athrepsia	10/24/20	7	4,150	W.L.M.	35.25	8.7
16	Athrepsia	10/11/20	1	2,500	Br. M.	8.5	3.4
17	Athrepsia	9/10/20	2	2,050	Br. M.	74.0	36.0
		9/11/20	2	2,050	Br. M.	27.0	13.1
18	Athrepsia	9/3/20	2½	2,800	Br. M.	51.0	18.2
		9/4/20	2½	2,900	Br. M.	51.0	17.5
		9/5/20	2½	3,000	Br. M.	51.0	17.0
19	Athrepsia	9/8/20	2½	2,700	W.L.M.	72.0	30.3
		9/9/20	2½	2,680	W.L.M.	30.0	11.1
		9/12/20	2½	2,600	W.L.M.	32.0	12.3
		9/15/20	2½	2,500	W.L.M.	36.4	14.5
20	Athrepsia	9/20/20	8	3,870	W.L.M.	68.8	18.0
		9/21/20	8	3,880	W.L.M.	94.3	24.2
		9/23/20	8	3,820	W.L.M.	89.1	23.0
21	Athrepsia	10/3/20	10	5,300	Prot. M.	158.2	29.8
		10/4/20	10	5,400	Prot. M.	180.0	33.3
		10/5/20	10	5,450	Prot. M.	125.0	22.9
		10/6/20	10	5,450	Prot. M.	63.0	11.5
		10/7/20	10	5,480	Prot. M.	127.7	23.2
		10/8/20	10	5,480	Prot. M.	133.7	24.3
22	Athrepsia	11/27/20	2½	2,980	Br. M.	33.7	11.3
		12/3/20	2½	3,050	Br. M.	42.5	13.9
		12/9/20	33	3,450	Br. M.	46.0	13.3
23	Athrepsia	12/14/20	5	3,200	Prot. M.	75.0	23.4
24	Athrepsia	12/14/20	4½	2,900	W.L.M.	37.0	12.7

TABLE XXVI. (*Continued*)

No.	Diagnosis	Date	Age Mos.	Weight	Feeding	Mg. total of Uric Acid	Mg. Uric Acid per Kg. body wght.
25	Athrepsia	12/24/20	1 ½	3,280	Prot. M.	82.6	25.1
		1/9/21	2	3,280	W.L.M.	57.7	12.5
		1/10/21	2	3,250	W.L.M.	35.1	10.8
		1/14/21	2	3,050	Br. M.	112.5	36.9
		1/18/21	2	3,080	Br. M.	65.5	21.6
		1/21/21	2	3,400	Br. M.	55.5	16.4
26	Athrepsia	3/17/21	3	3,680	Br. M.	197.0	53.5
		3/18/21	3	3,680	Br. M.	56.0	15.2
		3/19/19	3	3,680	Br. M.	51.0	13.5
		3/20/21	3	3,700	Br. M.	66.2	17.9
		3/21/21	3	3,780	Br. M.	86.0	27.7
		3/10/21	1 ½	2,420	W.L.M.	59.5	25.0
27	Athrepsia	3/11/21	1 ½	2,480	W.L.M.	39.0	15.7
		3/12/21	1 ½	2,500	W.L.M.	49.6	19.8
		3/13/21	1 ½	2,540	W.L.M.	54.0	21.2
		3/14/21	1 ½	2,560	W.L.M.	67.9	26.5
		3/12/21	3	3,620	Br. M.	42.0	11.6
		3/24/21	3	1,930	Br. M.	56.7	29.3
28	Athrepsia	3/25/21	3	1,920	Br. M.	37.7	19.1
		3/26/21	3	1,980	Br. M.	21.7	10.9
29	Athrepsia	3/27/21	3	2,000	Br. M.	23.0	11.5
		4/4/21	3	2,220	Br. M.	19.2	8.6
		4/5/21	3	2,110	Br. M.	16.90	8.0
		4/6/21	3	2,140	Br. M.	11.90	5.5
		3/21/21	5 ½	4,390	Br. M.	15.7	3.5
		4/1/21	5 ½	4,390	Br. M.	15.7	3.5

cock¹¹³. Amino acid nitrogen was determined by the van Slyke method¹¹⁴.

As far as creatinin is concerned, Hoogenhuyze and Verloegh¹¹⁵, Amberg and Morrill¹¹⁶ and Simon¹¹⁷ found that the creatinin nitrogen of the urine in infants ranged from 0.4 to 3.6 per cent. of the total nitrogen. Furaro¹¹⁸ has made the most complete investigation of this subject. He examined four normal breast fed infants and eleven infants suffering from various conditions, ranging in age from 3 months to 3 years, and found the total creatinin output per kilo of body weight in twenty-four hours to vary from 4.62 to 10.81 mg. He came to the conclusion that this output was influenced very little, if any, by the feeding and nutritional condition of the infant.

The results of my own studies appear in Table XXV.

It will be seen from Table XXV. that the creatinin output per kilo of body weight per day reached a high figure in the case of one infant suffering from cretinism (No. 6). In all the others the output ranged from 3 to 13 mg. The athreptic infants, as a group, showed no increase in creatinin in the urine as compared with the normal infants,

the amount of creatinin was indeed somewhat lower in the case of infants in very poor nutritional condition.

Few observations have been made on the uric acid excretion in infancy, Orgler¹¹⁹ found less excretion of uric acid by breast fed infants than by those artificially fed. This he attributes to the fact that breast fed infants can utilize food better than those artificially fed. A number of observations have been made on the uric acid output in newly born infants, but as the uric acid metabolism is different during this period than afterwards the results are of no special value for comparative purposes. In Table XXVI. are shown the results of seventy-four determinations made on thirty infants.

It will be seen that variations in uric acid excretion are large (1.5 to 40 mg. per kilo of body weight in twenty four hours). In a single case of acute diarrhea it was as high as 78 mg. per kilo of body weight. There seems to be no relationship between the uric acid output and the nutritional condition of the infant. It was high in the case of perfectly normal infants.

It has been generally assumed, without having any reliable figures on which to base the assumption, that the amino-acid excretion was increased in the severe nutritional disturbances. Bahrdt and Edelstein¹²⁰ found in infant's urine such varying results, that from their work it is impossible to come to any conclusion as to the excretion either in normal or pathologic cases. They found in one athreptic infant an amino-acid output of 10 per cent. of the total nitrogen. According to Hadlich and Grasser¹²¹ the amino-acid output is independent of the condition of the infant and bears no relationship to the feeding. In one condition both Simon¹¹⁷ and Hadlich and Grasser¹²¹ are in agreement as to an increased excretion of amino acids. This condition is "alimentary intoxication".

My own figures as a result of seventy-two examinations on thirty-one infants show that the amino-acid nitrogen output as expressed in the terms of percentage of total nitrogen excretion vary from 0.1 to 12 per cent. The highest figure in normal infants was 9.7 in one newly born infant. Otherwise the amount was not more than 4.1 per cent. In a very few instances athreptic infants show an increased excretion of amino-acid nitrogen but this was not at all constant.

It is thus seen that neither creatinin, uric acid nor amino-acids in the urine can account for the high carbon nitrogen and chloric nitrogen ratio in the athreptic infant. Other substances have therefore been considered.

10. *Organic Acids in the Urine.*

As has been previously mentioned, several observers have reported a high ammonia excretion in the urines of athreptic infants. This might be interpreted as evidence of increased excretion of acid but Keller was unable to find any increase in the organic acids of the urine; this was, perhaps, due to the fact that at time no entirely satisfactory method was available. Recently Van Slyke and Palmer¹²² have describ-

TABLE XXVII.

Amino Acid Output in 24 Hours.

No.	Diagnosis	Date	Age Mos.	Weight	Mg. Total N. in 100 Cc	Mg. Free Amino Acid N. in 100 Cc.	Per cent. Amino Acid N. of Total N.
1	Normal baby	2/11/21	18	9,300	556	7.3	1.3
		2/12/21	18	9,290	440	4.0	0.9
		2/13/21	18	9,280	664	2.5	0.3
2	Normal baby	2/11/21	13	10,100	348	2.4	0.6
		2/12/21	13	10,100	592	5.5	0.9
		2/13/21	13	10,100	1140	6.6	0.5
		11/26/20	2	5,300	420	5.5	1.0
3	Normal baby	1/3/21	2wk.	3,100	468	45.6	9.7
4	Newly Born	1/7/21	5	6,400	296	4.0	1.3
5	Normal baby	2/25/21	5½	6,500	248	7.4	3.0
6	Normal baby	2/28/21	5wk.	3,700	232	1.7	0.7
7	Normal baby	2/28/21	6wk.	4,000	192	8.0	4.1
8	Normal baby	3/1/21	6wk.	4,000	176	4.0	2.2
9	Normal baby	3/10/21	4wk.	3,560	264	6.0	2.2
10	Feeding Regulation	10/25/20	3wk.	2,750	176	6.0	2.2
11	Malnutrition	11/26/20	11	4,800	236	11.0	4.6
12	Malnutrition	12/24/20	14	6,600	520	5.5	1.0
13	Ileocolitis	11/30/20	18	5,400	520	18.7	2.6
14	Ileocolitis	11/30/20	9	5,600	360	36.0	10.2
15	Ileocolitis	12/2/20	9	6,200	268	25.0	9.3
16	Ileocolitis	12/15/20	8	6,000	420	12.6	3.0
17	Acute Diarrhea	12/14/20	3½	5,200	320	15.4	4.8
18	Acute Diarrhea	1/8/21	9	4,300	296	6.0	2.0
19	Pyloric Stenosis	12/9/20	4	2,620	400	3.3	0.8
20	Pyloric Stenosis	2/2/21	5	3,000	800	14.0	1.7
		1/3/21	2	2,600	264	5.5	2.0
		1/6/21	2	2,700	252	11.0	4.3
21	Athrepsia	10/16/20	11	6,100	664	15.4	2.3
		10/27/20	11	5,200	532	12.6	2.3
		10/28/20	11	5,150	332	11.0	3.3
22	Athrepsia	10/16/20	8	4,400	288	5.5	1.9
		10/16/20	8	4,300	520	1.1	0.1
		10/18/20	8	4,200	560	9.3	1.6
23	Athrepsia	10/27/20	2½	2,980	160	9.3	5.8
		12/9/20	3	3,450	204	5.5	2.6
		1/8/21	3½	4,000	280	9.3	3.3
		3/6/21	6	5,600	312	16.5	5.3
24	Athrepsia	3/8/21	6	5,600	348	11.8	3.1
		11/28/20	4	2,450	200	25.0	12.0
		12/14/20	4½	2,900	400	22.5	5.6
25	Athrepsia	12/14/20	5	3,200	560	15.4	0.5
26	Athrepsia	12/24/20	1½	3,280	360	3.8	0.9
27	Athrepsia	1/18/21	2	3,250	136	8.8	5.9
		1/21/21	2	3,400	120	3.8	3.2
		1/28/21	3	3,250	120	8.8	7.3
		2/1/21	3	3,300	112	5.5	4.9
		2/10/21	3½	3,450	148	6.6	4.5

TABLE XXVII. (Continued).

No.	Diagnosis	Date	Age Mos.	Weight	Mg. Total N. in 100 Cc.	Mg. Free Amino Acid N. in 100 Cc.	Per Cent. Amino Acid N. of total N.
28	Athrepsia	2/15/21	3 1/2	3,500	132	1.32	1.0
		2/17/21	3 1/2	3,440	324	1.7	0.3
		2/18/21	3	3,180	332	3.5	1.0
		2/19/21	3	3,200	308	18.7	6.0
		2/20/21	3	3,250	100	3.5	3.5
		2/28/21	3	3,400	104	8.8	8.4
		3/1/21	3	3,450	124	8.8	7.0
		3/2/21	3 1/2	3,500	152	11.8	7.7
		3/17/21	3 1/2	3,680	348	11.8	3.3
		3/18/21	3 1/2	3,680	208	6.6	3.1
		3/19/21	3 1/2	3,680	200	8.2	4.1
		3/20/21	3 1/2	3,700	160	10.2	6.2
		3/21/21	3 1/2	3,780	256	8.2	2.6
		3/10/21	1 1/2	2,420	304	8.2	2.6
29	Athrepsia	3/11/21	1 1/2	2,480	296	7.4	2.4
		3/12/21	1 1/2	2,500	380	10.2	2.6
		3/13/21	1 1/2	2,540	304	10.2	3.2
		3/14/21	1 1/2	2,560	216	7.4	3.4
		3/28/21	2	2,750	332	4.9	1.1
30	Athrepsia	3/29/21	2	2,680	212	2.7	1.2
		3/12/21	3	3,620	228	6.6	2.8
31	Athrepsia	3/24/21	3	1,930	172	9.0	5.2
		3/25/21	3	1,970	132	9.0	6.8
		3/26/21	3	1,980	160	15.0	9.3
		3/27/21	3	2,005	200	2.9	1.4

ed a method, which permits of a determination of the organic acids of the urine. They find the normal organic acid excretion of the adult is between 8 and 11cc. of tenth normal acid per kilo of body weight. On applying this method to infants I have found the organic acid excretion to be approximately the same as that found in adults. (Table XXVIII).

TABLE XXVIII.

No.	Diagnosis	Age Mos.	Weight	Total Organic Acid	Organic Acid per Kg. of body weight
1	Syphilis, Congenital	3½	2,800	13.2	4.7
2	Parenteral infection	9	7,100	124.2	17.4
3	Parenteral infection	13	6,600	126.0	19.0
4	Acute Diarrhea	3	5,200	88.0	17.0
5	Acute Diarrhea	9	4,570	78.0	17.0
6	Acute Diarrhea	9	4,300	170.0	41.5
7	Ileocolitis	9	5,600	74.8	11.7
8	Ileocolitis	4	5,050	30.0	5.9
9	Pyloric Stenosis	4	2,650	20.4	7.6
		4	3,000	22.5	7.5
10	Pyloric Stenosis	2	2,600	20.0	7.6
		2	2,700	30.0	4.1
11	Malnutrition	3	4,880	90.0	18.4
12	Normal Baby	20	10,200	735.0	6.8
13	Normal Baby	½	3,040	26.25	8.6
14	Normal Baby	5	6,300	80.70	12.8
15	Normal Baby	2	3,250	35.00	10.7
16	Normal Baby	2	3,690	46.8	12.4
17	Normal Baby	2	3,800	44.8	11.7
18	Normal Baby	1	4,430	32.3	7.2
19	Normal Baby	1½	4,500	50.4	11.2
20	Normal Baby	8	6,800	72.0	10.4
		8	6,900	56.4	8.1
21	Parenteral infection	16	12,000	52.8	4.4
		16	12,000	71.5	5.9
		16	12,000	122.5	11.0
		16	11,050	71.2	6.4

TABLE XXIX.

Total Organic Acid Output and Ammonia Coefficient of Infants Suffering from Athrepsia.

No.	Date	Weight	Age Mos.	Cc. Urine in 24 hours	Mg. total Nitrogen in 100 Cc. Urine	Mg. NH ₃ N. in 100 Cc. Urine	% NH ₃ N. of Total N.	Cc. total organic acid in 24 hrs.	Cc. total organic acid per Kg. of body wt.
1	11/27/20	2,980	2½	200	160	40.0	25.0	88.0	29.3
	12/3/20	3,050	2½	170	188	33.2	17.6	101.32	34.0
	12/9/20	3,450	3	200	204	33.2	16.2		
	1/8/21	4,000	3	450	280	30.0	10.7	76.5	91.1
2	3/6/21	5,600	6	500	312	15.0	4.8	70.0	12.5
	12/14/20	2,900	4½	100	400	24.0	6.0	13.3	4.5
	12/16/20	2,950	4½	285	80	40.0	50.0	114.0	38.0
	12/17/20	2,950	4½	500	80	16.0	20.0	175.5	58.0
3	12/18/20	3,000	4½	285	128	24.0	18.7	142.0	25.0
	12/19/20	3,050	4½	275	80	36.0	45.0	140.0	47.5
	12/20/20	3,050	4½	425	80	40.0	50.0	168.0	54.0
	1/24/21	3,200	3	125	200	26.0	13.0	57.0	18.0
4	1/28/21	3,250	3	180	120	20.0	16.6	68.0	21.2
	2/1/21	3,300	3	420	112	16.0	14.2	25.2	8.4
	2/10/21	3,450	3½	350	148	15.4	10.4	22.0	6.5
	2/15/21	3,500	3½	410	132	12.4	13.1	49.2	14.6
5	2/17/21	3,440	3½	380	324	33.2	10.2	53.2	15.2
	12/24/20	3,280	1½	285	300	44.0	12.2	71.2	21.2
	1/8/21	3,280	2	70	1320	66.0	5.0	70.0	21.5
	1/10/21	3,250	2	52	—	—	—	123.7	38.6
6	1/13/21	3,050	2	100	220	40.0	18.1	63.0	21.0
	1/14/21	3,080	2	300	320	56.0	17.0	60.0	20.0
	1/18/21	3,250	2	355	136	24.0	17.0	35.5	10.9
	1/21/21	3,400	2	300	120	20.0	16.6	30.0	9.0
7	1/25/21	3,500	2	312	144	20.0	13.8	15.0	4.3
	10/3/20	5,300	10	113	520	56.0	10.7	141.2	26.6
	10/4/20	5,400	10	360	372	60.0	16.1	136.0	25.1
	10/5/20	5,450	10	500	284	64.0	27.5	190.0	35.5
8	10/6/20	5,450	10	360	320	52.0	16.7	136.0	35.2
	10/7/20	5,480	10	550	320	48.0	15.0	115.0	20.2
	10/8/20	5,480	10	535	340	40.0	11.7	107.0	19.0
	3/10/21	2,420	1½	350	304	13.2	4.3	35.0	14.5
9	3/11/21	2,480	1½	275	296	25.6	8.4	98.0	39.5
	3/12/21	2,500	1½	320	380	16.0	4.2	96.0	38.4
	3/13/21	2,540	1½	290	304	20.0	6.5	75.4	30.0
	3/14/21	2,560	1½	367	216	32.0	14.8	95.4	38.1
10	3/28/21	2,750	2	319	332	14.0	4.2	26.5	27.8
	3/29/21	2,680	2	244	212	27.8	13.1	53.6	20.0
	2/18/21	3,180	3	320	332	47.0	13.8	74.2	26.0
	2/19/21	3,200	3	210	308	40.0	13.0	72.0	24.0
11	2/20/21	3,250	3	430	100	27.4	27.4	51.6	16.0
	2/28/21	3,400	3	500	104	16.0	15.3	90.0	26.4
	3/1/21	3,450	3	620	124	16.0	12.9	74.0	21.8
	3/2/21	3,500	3	580	152	18.0	11.9	58.0	16.5

TABLE XXIX. (Continued).

No.	Date	Weight	Age Mos.	Cc. Urine in 24 hours	Mg. total Nitrogen in 100 Cc. Urine	Mg. NH ₃ N. in 100 Cc. Urine	% NH ₃ N. of Total N.	Cc. total organic acid in 24 hrs.	Cc. total organic acid per Kg. of body wt.
8	3/17/21	3,680	3½	346	348	37.6	9.7	83.0	22.5
	3/18/21	3,680	3½	425	208	78.0	23.0	59.5	16.1
	3/19/21	3,680	3½	300	200	25.0	19.5	36.0	9.8
	3/21/21	4,390	5½	100	248	21.8	8.8	20.0	4.5
9	4/1/21	4,390	5½	217	180	18.8	10.4	56.4	12.8
	3/24/21	1,930	3	180	172	38.8	20.2	68.4	35.4
	3/25/21	1,970	3	134	132	21.8	16.5	62.2	31.0
	3/26/21	1,980	3	290	160	25.0	15.6	63.8	32.2
10	3/27/21	2,000	3	303	200	22.4	11.2	30.2	15.1
	4/4/21	2,220	3	244	260	26.0	10.0	117.12	52.7
	4/5/21	2,110	3	138	208		12.0	38.6	18.3
	4/6/21	2,140	3	176	240	20.4	8.0	59.8	27.8
	4/14/21	2,600	3	268	376	26.4	6.2	75.04	28.8
	4/15/21	2,600	3	287	352	20.0	5.6	74.6	28.7
	4/18/21	2,660	3	308	320	23.0	7.2	61.6	23.1
	4/19/21	2,620	3	221	176	40.0	22.7	66.3	23.2
	4/20/21	2,850	3	232	248	33.0	13.3	74.2	25.5
	4/21/21	2,900	3	279	236	28.4	12.0	72.5	24.9

Infants suffering from acute diarrhea show a considerable increase in the excretion of organic acids. On applying the same method to the urines of a number of athreptic infants a considerable increase in organic acid excretion was found in every instance. (Table XXIX).

The ammonia in the urines of these infants was also determined (Folin's method¹²³⁻¹²⁴). A high excretion of ammonia was found as compared with normal infants and this ammonia excretion was, in a general way, proportionate to the amount of organic acids in the urine. From this one would be led to suppose that the high ammonia coefficient was directly the result of the increased organic acids.

With improvement in the infant's general nutritional condition, both organic acids and ammonia of the urine approach normal levels. This is shown graphically in Fig. 9 and Fig. 10.

The next question which arises is as to the nature and source of these organic acids. One might suspect that they were acids of the acetone body series excreted on account of partial starvation. Another possibility would be that they were acids produced from the bacterial decomposition of carbohydrate and fats in the gastro-intestinal tract and absorbed and excreted unchanged. These acids might also represent incompletely metabolized products of any of the three main foodstuffs.

In order to determine the effect of the fat intake on the excretion of organic acids in the urine, an athreptic infant, who during a four day period excreted 28, 28, 23, 23, Cc. of tenth normal organic acids

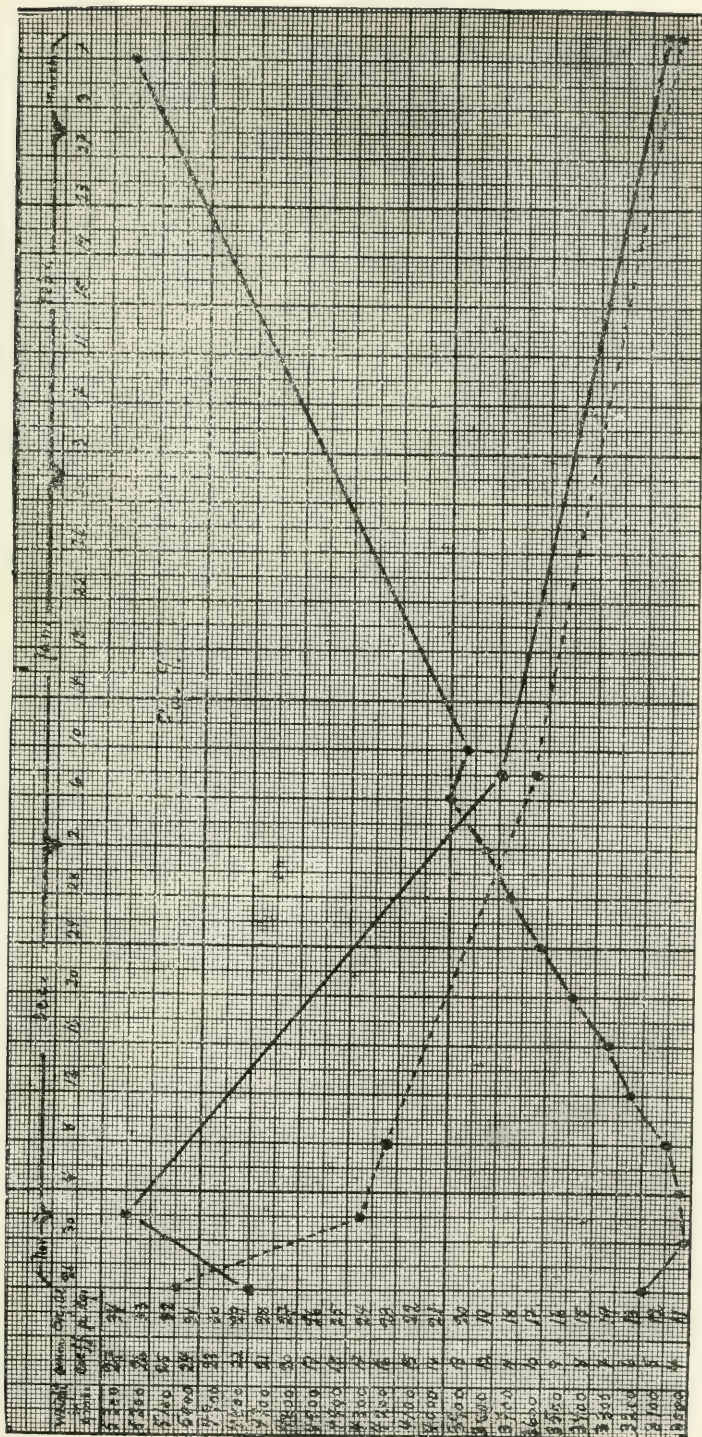


FIG. 9.

This chart shows relationship between the nutritional condition, organic acid excretion in the urine and ammonia coefficient.

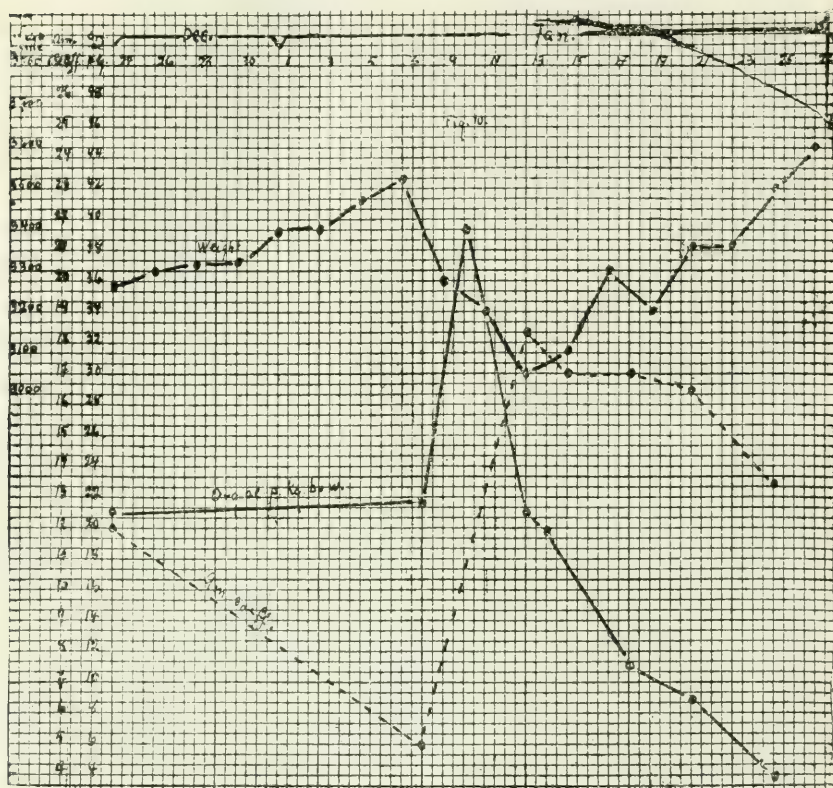


FIG. 10.

This chart shows relationship between nutritional condition, organic acid excretion in the urine and ammonia coefficient.

in the urine per kilo of body weight, while on a formula containing 1.6 per cent. of fat was fed on a mixture otherwise the same but containing 4.3 per cent. fat. On this high fat feeding the volatile fatty acids in the stools increased from 85 cc. of tenth normal acid to 112 cc. The organic acid output in the urine remained, however, practically the same; that is to say, 24 Cc. tenth normal acid per kilo of body weight. The ammonia coefficient was also unchanged. Another infant 16 months of age, suffering from otitis media, but in good nutritional condition was fed on a milk mixture containing 1.9 per cent. fat excreted 4.5 and 5.9 Cc. of tenth normal organic acid on two consecutive days. The fat in the food was then increased to 4.8 per cent. the other constituents remaining the same, and the child excreted 11.1 and 6.4 Cc. of tenth normal organic acid per kilo of body weight per day. The ammonia coefficient on the low fat days ran from 3.1 to 4 per cent.; on the high fat days 4.2 and 4.5. We thus see a relatively

small increase in the excretion of organic acid and of ammonia following a great increase in the fat of the diet. A third infant (athreptic) was carried over three weeks metabolism experiment. Received the first week 1.6 per cent. fat, the second week 3.5 per cent. fat, third week 4.8 to 5.4 per cent. fat. The total organic acids in the urine remained practically unchanged. Showed variations up to 12 cc. per kilo of body weight, that is within normal limits. The ammonia coefficient was not influenced by the fat in the feeding. These results are not comparable to those of Howland and Cooke¹²⁸ who found an increase in the ammonia of the urine of infants receiving 7-8 per cent. fat.

Mention has already been made of the fact that there is an insufficient amount of amino-acids in the urine to account for the large amount of organic acids present. Most of the common organic acids, particularly those of the fatty acid series, are soluble in ether. In an attempt to separate these acids from the urine for further identification, the urines of these infants were extracted with ether with the result that only about 20 per cent. of the acids present were extractable. The nature of these organic acids which are insoluble in ether has not yet been determined. Certainly they are not acids of the acetone body series nor lactic acid.

Last year (1922) the urine of several athreptic infants were examined for oxyproteic acids. Normal infants excrete about from 1 to 1.5 per cent. of the total nitrogen in the form of oxyproteic acid nitrogen. In the case of athreptic infants the oxyproteic acid nitrogen may be as high as 10 per cent. of the total nitrogen. The average was about 5 per cent. The method of determination was that of Ginsberg¹²⁶. This, possibly, does not account for all the acids present in the urine of these infants, but it will explain some of them.

From the evidence at hand we can only assume that these acids are the result of a disturbed metabolism, and represent products which would under normal conditions be completely broken down. Such a disturbance of metabolism would, if continued over a considerable length of time, naturally effect the nutrition. The evidence is that the cause of the disturbed metabolism is deep seated and that many of the cells of the body are involved. It would not seem unreasonable that the cells of the gastro-intestinal tract also suffer. If the poor circulation, which has been found to occur in the peripheral parts of the body of these infants, were also present in the gastro-intestinal tract, it would contribute to increase the pathological changes in the cellular function of the intestinal tract. The importance of the circulatory factor in these conditions has been emphasized. With a lowered functional capacity of the cells of the gastro-intestinal tract the power of absorption would naturally be lowered.

11. *Absorption of Food from the Intestinal Tract.*

In order to obtain some idea of the absorptive power of the intestinal tract of these infants, some determinations of the total caloric intake and output have been made (Table XXX).

TABLE XXX.
Caloric Intake and Loss in 24 Hours

No.	Diagnosis	Date	Weight	Age Mos.	Total Cal. Intake	Total Cal. Stools	Total Cal. Urine	% Total Cal. Loss of Intake
1	Athrepsia	4/25/21	2,600	1½	326	81	5.6	26.5
		5/15/21	2,750	2	385	37	2.62	10.5
2	Athrepsia	5/16/21	2,800	2	296	19	2.96	7.4
		2/ 1/21	3,300	3	399	45	5.04	12.2
		2/10/21	3,450	3	453	59	6.40	14.3
3	Athrepsia	2/15/21	3,500	3	440	18	8.11	6.0
		2/ 7/21	2,530	1½	866	161	1.88	19.0
4	Athrepsia	2/18/21	3,180	3	594	34	14.16	18.2
		2/19/21	3,200	3	521	92	8.17	19.1
		2/20/21	3,250	3	534	60	9.04	13.0
		2/28/21	3,400	3	481	66	5.99	7.6
		3/ 2/21	3,500	3	455	31	7.52	8.5
		3/17/21	3,680	3½	674	41	8.64	7.4
		3/18/21	3,680	3½	674	45	4.60	7.4
		3/19/21	3,680	3½	490	45	3.60	9.9
		3/20/21	3,700	3½	461	28	8.40	7.9
		3/21/21	3,780	3½	540	35	7.82	8.0
		3/10/21	2,420	1½	376	53	5.0	15.4
		3/11/21	2,480	1½	376	49	4.4	14.4
		3/12/21	2,500	1½	326	54	6.7	18.7
		3/13/21	2,540	1½	387	43	4.7	13.3
5	Athrepsia	3/14/21	2,560	1½	274	45	6.9	19.0
		3/28/21	2,750	2	336	30	6.6	10.9
		3/29/21	2,680	2	292	41	6.07	16.0
		3/24/21	1,930	3	426	80	6.40	20.4
		3/25/21	1,970	3	321	80	3.00	22.5
		3/27/21	2,000	3	261	58	7.22	22.2
6	Athrepsia	4/20/21	2,850	2	448	79	6.75	19.3
		5/ 7/21	12,000	16	661	81	30.3	16.8
		5/ 8/21	12,000	16	593	66	30.0	16.2
7	Parenteral Infection	5/ 9/21	12,000	16	846	61	44.0	11.3
		3/ 2/21	2,400	5	537	32	13.0	8.4
		2/ 5/21	2,400	5	981	50	13.9	6.5
8	Pyloric Stenosis	5/ 2/21	6,880	8	865	60	19.7	9.17
		5/ 3/21	6,880	8	945	32.4	22.8	5.8
		5/ 4/21	6,900	8	904	78	25.6	11.4
9	Normal baby							
10								

The total caloric intake and output of ten infants were examined. One of the infants was convalescing from pyloric stenosis and one

was suffering from a parenteral infection. One was perfectly normal and the seven others were in a condition of more or less advanced athrepsia. In all but one instance the experiment was carried over a number of days. Combustion of the urine and stools was made in the Riche bomb calorimeter in the manner described above. The total caloric value, and not the physiological value was considered. The results appear in Table XXX. From this it will be seen that the normal infants studied as well as the one with pyloric stenosis, who was in a fair condition, showed a figure approximating those previously determined on normal infants. For example Rubner and Heubner found a total caloric loss which was 7.3 per cent. of the caloric intake. The seven athreptic infants all showed a greatly increased loss of the combustible material in the excreta, in one instance as high as 26 per cent. of the total intake. With improvement in the general condition of the infants, there was a much lessened loss of material, in some instances the loss falling to entirely normal figures after a period of improvement. In Fig. 8. is shown graphically the relationship between gain and weight, caloric loss in the stools and the caloric nitrogen ratio of one of these infants (Number 4.) The question of substance lost by way of the intestinal tract, then arises.

This led us to perform some complete metabolism experiments on athreptic infants determining not only organic constituents but also the inorganic constituents.

12. *Complete Metabolism Studies in Athreptic Infants.*

(a) *Fat Metabolism.*

The most striking feature of such an infant is the nondeposition of fat in the tissues. For this reason many inquiries have been directed toward the fat metabolism. It is especially the fat absorption which has been discussed.

It is difficult from the literature to come to any definite conclusion as to the fat absorption in the athreptic infants. The percentage absorption given by various authors show great variations. The experiments done by Rubner and Heubner¹²⁷ on a 3½ months old infant weighing 3035 gm. showed an absorption of 84.5 per cent. of the fat when on a milk diet. On a carbohydrate diet the absorption was only 56.9 per cent.

Bendix¹²⁸ obtained a fat absorption figure of 59 per cent. on an athreptic infant. L. F. Meyer¹²⁹ states that the per cent. absorption for fat in a 3 months old athreptic infant was for five periods 74.2 per cent., 24.9 per cent., 51 per cent., 68.3 per cent., and 78 per cent. respectively. Fife and Veeder¹³⁰ in two cases of athrepsia found the absorption to be less than in healthy children. On the other hand, W. Freund¹³¹ gives for three athreptic infants an absorption of 90 per cent., 97 per cent., and 81.8 per cent., figures, which do not vary much from normal figures, which are from 92 to 95 per cent.

Recently Hutchison¹³² has found the average fat absorption in athreptic infants to be about 73 per cent. He assumes that

the fat excreted always forms $1/3$ of the total fecal weight (dry feces) and that the percentage absorption will depend upon the fat intake and the fecal weight. When the intake is over 20 gm. in 24 hours, the difference in intake may for practical purposes be neglected, and the fat absorption will depend almost entirely on the fecal weight. In a series of 22 normal and 22 athreptic infants he found 98.4 per cent. absorption in the normal infants and only 73.5 per cent. in the athreptic group. He attributes this low value to the low fat intake in these latter cases. This averaged 17.8 gm. in 24 hours, as compared with 35 gm. in the normal infants.

Holt, Courtney and Fales¹³³, on the other hand, have shown that the total fecal fat does not always form a constant part of the dry feces. Their average figure is 34.5 per cent. but frequently it was found as high as 50 per cent. of the fecal weight. Furthermore, they found no constant relationship between the percentage of fat in the mother's milk and the percentage of total fat and its distribution in the stools. The same authors¹³⁴ found an average absorption of fat in infants suffering from chronic intestinal indigestion to be 79.1 per cent. in alkaline stools and 77.7 per cent. in acid stools. Their own figures for fat absorption in normal infants were 90.3 to 99.2 per cent.

Passing to my own material it is seen from Table XXXI. that the fat absorption has been examined in 13 athreptic infants in most of them in 5 and 4 day periods. The percentage fat absorption varies from 41 to 93 per cent. with an average of 77 per cent. Results are expressed in terms of total fatty acids.

The average intake is 19.5 gm. with an average output of 4.65 gm. in 24 hours. The weight of stools has not been determined, as evaporation to dryness was omitted on account of fear of loss of nitrogen, which was determined at the same time. According to Hutchison difference in intake in my cases should have little or no effect on the output as the intake in this series lies very close to 20 gm. (19.5). Still, the average absorption is not more than 77 per cent., that is considerably below normal.

It seems reasonable then to believe that the high caloric loss through the intestinal tract found as stated above in athreptic infants is at least partly due to the low fat absorption in these infants.

(b) *Carbohydrate Metabolism.*

Fleming¹³⁵ has recently performed some respiratory exchange experiments on infants suffering from athrepsia, in order to find out the nature of the metabolism and the quantity of the material metabolized. His conclusion is that the experiments show that, in athrepsia, the essential constituents of the diet can all be normally utilized and by exclusion (referring to Hutchison's article on fat, and taking for granted that nitrogen metabolism is normal) he assumes a poor absorptive power of the intestinal tract for carbohydrate. This he considers the main feature in the picture of athrepsia.

There seems to be no figures in the literature which indicate that

TABLE XXXI.

Fat Absorption in Athreptic Infants.

Case No.	Weight Gms.	Age	Feeding	No. of Exp. days	Consist of stools	Aver. fat intake in 24 hr.	Aver. fat output in 24 hr.	Per Cent. Absorption
1	2,600	3 weeks	W.L.M.	1	Semif.	19.1	11.2	41
	2,700	5 "	Br. Fed	5	Semif.	19.1	4.2	78
2	2,600	6 "	W.L.M.	2	Semif.	12.9	3.2	77
	2,660	7 "	W.L.M.	5	Semif.	13.9	3.3	76
	3,100	8 "	W.L.M.	2	Loose	17.1	5.0	79
3	1,930	3 months	Br. Fed	4	Semif.	20.0	4.6	77
	2,060	3 "	Br. Fed	5	Semif.	19.4	2.72	86
4	2,760	2 "	W.L.M.	2	Semif.	9.7	2.6	74
9	5,100	9 "	W.M.Mixt.	5	Formed	20.5	2.8	86
10	5,500	10 "	W.M.Mixt.	5	Formed	22.5	8.5	62
11	5,800	5 "	W.M.Mixt.	4	Formed	26.3	4.2	84
	5,800	5 "	W.M.Mixt.	2	Loose	42.7	7.1	83
12	2,400	6 weeks	Br. Fed	4	Semif.	11.0	8.5	81
13	2,600	6 months	Br. Fed	5	Semif.	17.1	2.6	84
14	2,250	5 weeks	Br. Fed	5	Semif.	16.0	1.1	93
15	1,800	6 "	Br. Fed	5	Semif.	14.3	2.1	85
17	3,000	5 "	W.L.M.	5	Watery	9.8	5.40	45
	3,100	6 "	W.L.M.	5	Firm	22.5	3.6	84
	3,400	7 "	W.L.M.	5	Firm	33.0	4.5	86
18	3,100	3 months	W.L.M.	4	Watery	20.0	4.0	80
		Average..	19.5	4.60	77

such a failure in absorption of carbohydrate actually takes place. Usuki¹³⁶ studied eight infants of whom three may be considered athreptic. All his infants show a percentage loss of intake of not more than 0.1 to 1.9 per cent. and the infants in a poor condition not more than others. Heubner¹³⁷ described a very emaciated three and a half months old infant weighing 2,730 gm., in which the ability of digesting and absorbing the carbohydrate was tested. He states that of 40 gm. starch in the form of rice, only 0.16 gm. were found in the stools. The infant died directly after the experiment and the dry content of the small intestine amounted to 2.05 gm. with only traces of starch. The large intestine contained only 0.136 gm. starch. He concludes from this finding that absorption of starch takes place chiefly in the small intestine and furthermore that absorption of carbohydrate even in an athreptic infant takes place immediately after transformation to sugar. Heubner's second case was also a very emaciated infant, one year of age, in whom the starch utilization was 99.7 per cent.

It must, of course, be recognized that a certain amount of unabsorbed carbohydrate is broken down by bacterial action, chiefly in the lower bowel. For this reason the determination of carbohydrate in the stools does not actually indicate the extent of carbohydrate ab-

sorption. The figures should, however, indicate in a general way, whether or not lack of absorption occurs.

The carbohydrate output has been examined in seven athreptic infants over five day periods. (Table XXII).

TABLE XXXII.

Excretion of Carbohydrate in Athreptic Infants.

No.	Feeding	Weight Gms.	Age	Consist. of stools	No. of Exp. days	Aver. Intake	Aver. Output	Per cent. excretion of intake
1	Br. M.	2,250	6 wks.	Semif.	5	33.5	0.26	0.80
2	W.L.M.	3,000	5 "	Watery	5	37.5	0.34	0.93
	W.L.M.	3,150	6 "	Semif.	5	39.4	0.10	0.26
3	Br. M.	2,250	5 "	Semif.	3	33.7	0.20	0.60
4	Br. M.	1,750	5 "	Semif.	5	23.5	0.17	0.73
5	W.L.M.	3,150	3 mos.	Watery	5	78.0	0.53	0.67
6	Br. M.	3,200	3½ "	Watery	5	52	0.46	0.88
7	W.L.M.	2,100	3 "	Watery	2	46	0.45	0.97

The sugar output was in all cases very small, not exceeding one per cent. of the intake, regardless of the consistency of stools. One of the infants, No. 5, was fed on a high sugar diet, 12.4 per cent. sugar in an undiluted whole lactic acid milk. The stools were watery, but the carbohydrate excretion was only 0.67 per cent. of the intake.

It seems then that the high caloric output in the stools of some of these infants cannot be explained on the basis of insufficiency of carbohydrate digestion and absorption.

(c) Protein and Salt Metabolism.

Both Czerny and Finkelstein have considered a demineralization an essential factor in the pathogenesis of athrepsia.

The literature on nitrogen and salt metabolism in athrepsia is not very extensive. Heubner and Rubner's¹²⁷ original and fundamental metabolism study in 1899 on a 7 months old normal and a 3½ months old athreptic infant where fat, nitrogen, and total ash were determined showed following results, expressed as per cent. loss of intake through intestinal tract:

<i>Normal Infant.</i>			<i>Athreptic Infant.</i>		
N.....	6.38	%	N.....	18.27	%
Fat.....	3.5	%	Fat.....	15.54	%
Ash.....	35.9	%	Ash.....	45.45	%

It was mainly on this experiment that Heubner founded his theory of athrepsia, as mainly due to a lack of absorption of food from the intestinal tract.

Blauberg¹²⁸ made a complete salt determination on the same infants

used by Heubner and Rubner. The athreptic infant when fed on a usual whole milk mixture showed a positive salt balance except for Cl and SO_3 , and a negative balance for all salts when on a thin cereal feeding. The normal infant showed a negative sodium chloride and SO_3 balance. All experiments were done over three day periods.

Steinitz²⁸ in 1903, found an increase of the ammonia coefficient with a decreased alkali excretion in the urine and a correspondingly increased output in the stool after high fat feeding.

L. F. Meyer¹²⁹ in 1910 examined three athreptic infants and came to the conclusion that the condition of the infants, and especially the character of the stools, determined the quality of loss of the mineral salts. In the stage of "Bilanzstörung" he found a negative calcium balance, as long as soap stools were passed. In the stage of "Dekomposition" when the stools were diarrheal, alkalies especially were lost. Nitrogen balance was negative in two cases, positive in one. He considers the nitrogen loss as a result of the salt loss.

Marfan, Dorlencourt and Saint Girons¹³⁰ have determined the total ash metabolism on a 3 months old athreptic infant, weighing 3510 gm. over a period of 7 days. They found a negative total ash balance. Individual constituents were not determined. These authors believe a deficiency of enzymes in the cow's milk to be the cause of this negative salt balance, and that the cells of the organism have lost their power of utilizing the salts.

Jundell¹⁴⁰ examined two dyspeptic infants and two infants suffering from intoxication. The first dyspeptic infant, one month old, weighed 3400 gm. and lost 40 gm. in the 5 days period. This infant showed a positive nitrogen and salt metabolism except for sodium. In the next period with a loss of 140 gm. there was a good retention of nitrogen as well as of all salts. The other dyspeptic infant, 3 months old, weighed 4300 gm. and was examined over five periods. In the first period, with unchanged weight, there was a good retention, except for chloride. In the next two day period, with a gain of 100 gm. a negative phosphate, sodium and chloride retention occurred. In the third period, with loss of 250 gm., there was a negative phosphate, potassium and chloride balance. In the fifth five day period, with a loss of 80 gm. a negative sodium and chloride retention occurred. The absorption was good for all constituents.

My own experiments have usually extended over five day periods. Some infants have been examined for several periods in different stages of their nutritional condition. Nitrogen, fat, carbohydrate, chloride, phosphate, calcium, potassium and sodium have been determined for nearly all of them. (For the technic see "Methods".) Total nitrogen determinations were done on nineteen infants. Nitrogen plus salts on fourteen infants, of whom thirteen were athreptic and one a normal infant. All infants have shown a normal temperature during the whole period. The material follows:

Case No. 1.—3 weeks male infant. Admitted 4/20/21. Admission weight 2560 gm.

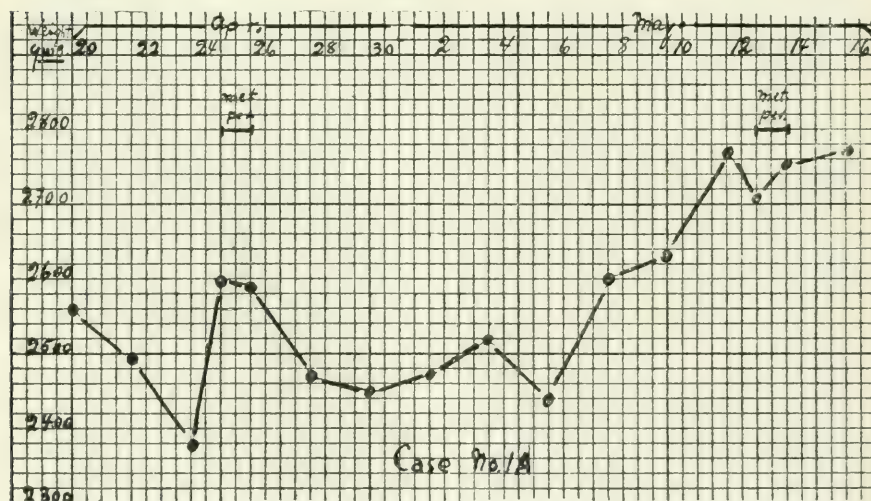
F. H. — Mother sick in hospital, cause unknown.

P. H. — Full term normal baby. Was never breast fed. Birth weight unknown.

P. I. — Failure to gain. Has been fed on whole milk, 360 cc., water 360 cc., sugar 30 gm., but does not take feeding well. Stools have never been loose. Weight stationary since birth.

Ph. Ex. — Patient is an extremely small and undernourished infant of three weeks. Features pinched, eyes sunken, color gray, skin over body very loose and dry, abdomen distended. There are enlarged inguinal glands present. Extremities very wasted. Mucous membranes show a good color. The throat, ears, lungs, and heart negative. No enlargement of internal organs. Von Pirquet and Wassermann reaction negative. Urine normal.

Course in Hospital. — The infant was given several intraperitoneal and intravenous injections with good effect. After fourteen days in hospital the infant started to gain weight and was two months later discharged in a fairly good condition.



Number	Grams Weight in	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
1	2600	3 wks	w.l.m.	1	Semif.	-10	CaO	0.88	0.002	2.136	1.256	0.	—
"	"	"	"	"	"	"	N.	0.97	0.512	0.588	-0.13	40.0	—
1	2700	5 "	Br. m.	1	Semif.	+50	N.	0.785	0.396	0.126	+0.263	83.8	33.5

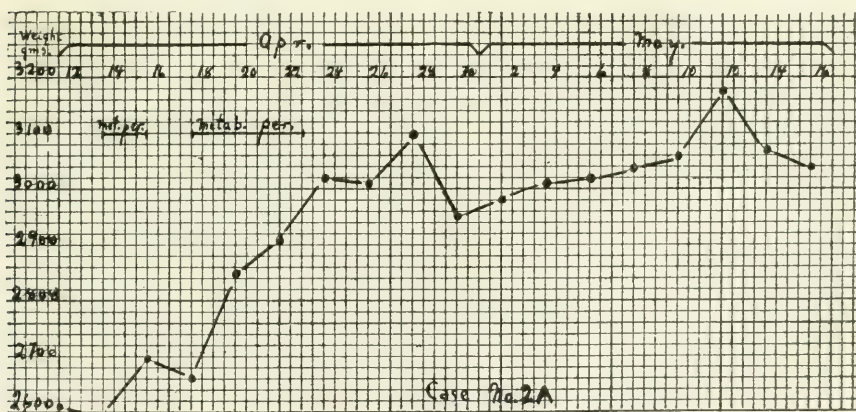
Case No. 2. — 6 weeks male infant. Admitted 4/12/21, weight 2600 gm. F. H. — unknown.

P. H. — Nothing known, patient is a foundling. Has been in an orphan's home for the past few days.

P. I. — Failure to gain weight.

Ph. Ex. — Very undernourished infant. Skin is dry, pale, mottled with no subcutaneous fat. Enlarged inguinal glands. Throat and ears negative. Heart negative. Lungs show crackling rales at both bases. Abdomen distended, but no masses felt. Von Pirquet reaction and Wassermann reaction negative. Urine normal.

Course in Hospital. — Patient was fed on whole lactic acid milk 360cc., water 200 cc., Karo syrup 50%, 70 cc. Gained on this formula the first fourteen days in hospital. Since then weight curve became practically horizontal, and remained thus until discharged, two and one half months after admission. Readmitted 8/18/21 on account of an infectious dermatitis, weight 3580 gm. Gain this time was not seen before the infant was given 180 calories per kilo of body weight. Discharged in a good condition.



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion in 24 hours.	Average Excretion in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
2	2600	6 wks	w.l.m.	2	+100	Semif.	N.	1.082	1.008	0.313	-0.239	71	—
							CaO	1.262	0.091	1.125	+0.046	10	3.6
2	2660	7 wks	w.l.m.	5	+250	Loose	N.	1.300	0.580	0.276	+0.444	79	34.0
							CaO	0.676	0.025	0.959	-0.308	0	—

Case No. 3.—3 months female infant. Admitted 3/16/21. Weight 2080 gm.

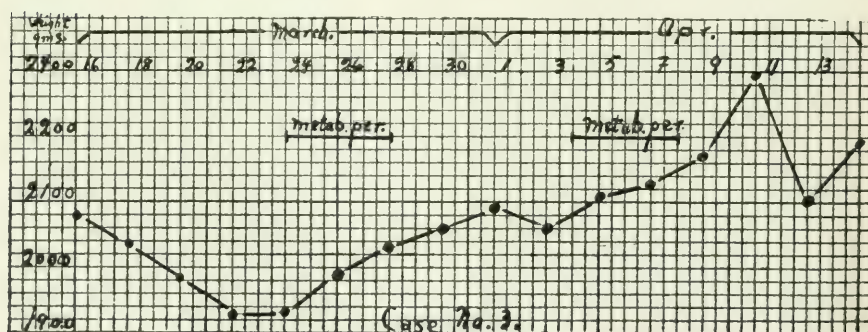
F. H. — Negative.

P. H. — An illegitimate full term infant, normal at birth. Was breast fed the first days of life. Mother was working and had to stop nursing.

P. I. — Started when infant was one month old. Patient would not gain weight, and developed a conjunctivitis, which became gradually worse with formation of an ulcer corneæ bilateralis.

Ph. Ex. — An extremely poorly nourished infant. Temperature sub-normal. Pulse and respirations slow. There is a bilateral corneal ulcer with a muco-purulent discharge from both eyes. Throat, ears, heart, lungs negative. Abdomen very much distended. No internal organs palpable. Von Pirquet and Wassermann reaction negative. Urine normal. Inguinal glands enlarged.

Course in Hospital. — The infant was given cow's milk mixture to start with but would not gain. Condition was extremely poor. The feeding was changed to one of breast milk. After a few days the weight curve began to go up. Both corneæ were completely destroyed but the nutritional condition of the infant improved greatly and the patient was discharged in a good nutritional condition.



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
3	1930	3 mos	Br. M.	4	Semif.	+100	N.	0.955	0.387	0.22	+0.348	77	36.5
3	2060	3 mos	Br. M.	4	Semif.	+60	N.	1.60	0.38	0.405	+0.815	74.7	51
"	"	"	"	"	"	"	CaO.	0.678	0.041	0.917	-0.280	0	—

Case No. 4. — 2 months old female infant. Admitted 3/10/21. weight 2430 gm.

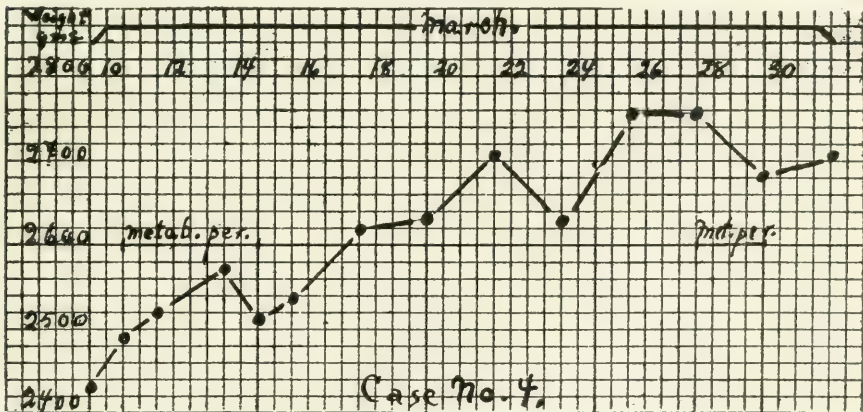
F. H. — Negative.

P. H. — Full term, normal baby. Birth weight 6 pounds. The infant has been on Eagle Brand since birth with very irregular feeding time.

P. I. — Weight has gone down since birth. Stools have been constantly loose. The infant has vomited off and on ever since birth.

Ph. Ex. — Very small wizened up baby. Face covered with wrinkles. There is no subcutaneous fat on body. Sucks hands constantly. Skin over abdomen and chest covered with silvery scales on reddened background. Inguinal glands enlarged. Throat, ears, heart and abdomen negative. Over lungs are heard some fine rales at both bases. Von Pirquet and Wasserman neg. Urine normal.

Course in Hospital. — Infant was fed on a whole milk mixture and did very well. Discharged in an improved condition 4/2/21.



Number	Weight in Grams.	Age	Feeding	Number of exp. days.	Consistency of stools	Loss or gain in grams.	Constituents examined.	Average intake in 24 hours.	Average excretion urine in 24 hours.	Average excretion stools in 24 hours.	Balance	Percentage absorption	Percentage retention
4	2430	2 mo.	w.l.m.	4	Semif.	+20	N.	1.600	0.92	0.40	+0.28	75.0	17.5
4	2760	2½ mo.	w.l.m.	2	Semif.	-80	N.	1.90	0.77	0.53	+0.60	72.0	31.5

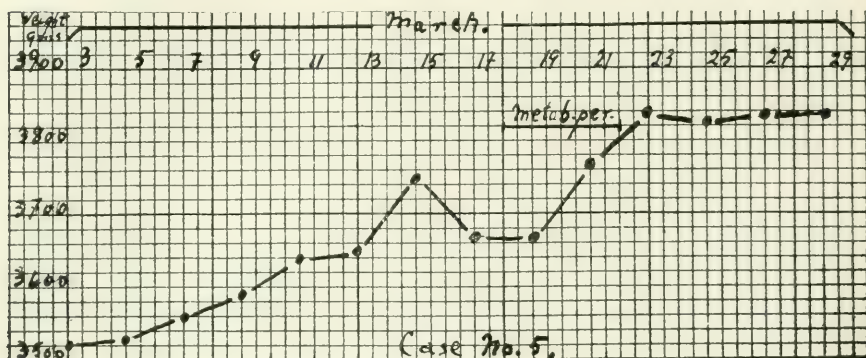
Case No. 5. — 3 months male infant. Admitted 2/17/21, weight 3070 gm.

F. H. — Negative.

P. H. — Very little is known. Has never been breast fed and has lost weight constantly since birth. Has constantly vomited and stools two to three times daily, gray with curds.

Ph. Ex. — A markedly athreptic infant. Skin dry, loose, of a pale grayish color. Slightly enlarged inguinal glands. Otherwise no glandular enlargement. Throat, ears, heart negative. Abdomen very distended, but no masses or internal organs palpable. Von Pirquet and Wassermann reaction negative. Urine normal.

Course in Hospital. — Baby was fed on whole lactic acid milk and gained weight. Stools normal. Discharged in good condition 4/14/21.



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
5	3410	3 mos	B.M.	4	Form.	+130	N.	1.91	0.88	0.37	+0.66	80.6	34.7

Case No. 6. — 13 months male infant. Admitted 8/27/21. Weight 5880 gm.

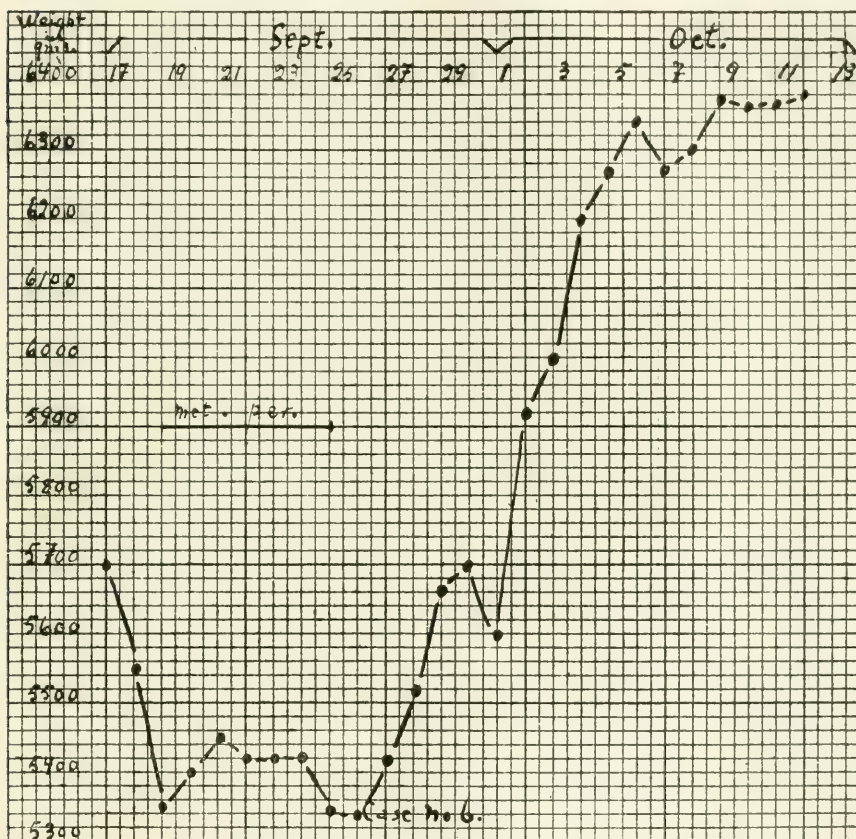
P. H. — Birth weight 9 lbs. Breast fed for 6 months, then put on whole milk formula.

P. I. — Vomiting and loose stools 3 weeks ago. 8-9 stools daily. No blood has been noticed in stools. For last three weeks baby has been running a temperature up to 102.

Ph. Ex. — An extremely poorly nourished and pale male infant. Weak cry, no panniculus. Moderate degree of aphthous stomatitis present. Enlarged cervical and inguinal glands. Heart and abdomen negative. Some coarse rales throughout both lungs. Von Pirquet and Wassermann reaction negative. Urine negative.

Course in Hospital. — Patient was constipated and gained on whole lactic acid milk and Karo syrup. Was discharged to the Out Patient Department 9/1/21 but diarrhea started again and he was readmitted to the hospital 9/17/21. Weight 5700 gm. Patient was then in a very miserable condition. Was very restless and pale. Features pinched

Skin loose and dry. Mucous membranes of mouth red. Heart, lungs, abdomen negative. Infant given whole milk and put on metabolism frame. Weight was horizontal and stool watery throughout metabolism



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
6	5450	14 mo.	W. M.	6	wat'y	5	N.	3.82	2.82	1.53	-0.53	60.	—
							Cl	0.34	0.237	0.185	-0.082	45.5	—
							P.	0.45	0.060	0.228	+0.162	49.8	36
							CaO.	0.82	0.007	0.820	-0.007	0.	—

period. When taken off the frame the infant was given infant diet on which he gained weight and had normal stools. Discharged from the hospital 10/17/21 considerably improved.

Case No. 7.—18 months male infant. Admitted 9/3/21. Weight 8,100 gm.

F. H. — Negative.

P. H. — Normal full term baby. Breast fed plus supplementary feeding for 12 months. For last month has been on mixed diet and Eagle Brand.

P. I. — During last five months has had constant attacks of vomiting and diarrhea. Bowel movements at present normal, 3 times daily. Four days ago a swelling started on both sides of neck.

Ph. Ex. — Very pale undernourished and restless infant. Looks sick. Tonsils enlarged, but not acutely inflamed. Cervical glands on both sides enlarged, tender tense and warm. Heart, abdomen negative. A few sonorous rales are heard over both lungs. There is a slight beading of ribs. Otherwise physical examination negative except for the very poor nutrition. Von Pirquet and Wassermann negative. Urine contained some WBC.

Course in Hospital. — Temperature on admission 38.5°C. which went down to normal after two days.

9/13/21 Weight going constantly down. No fever. Glands less swollen.

9/20/21 Steady loss of weight. Temperature normal. Stools loose.

9/24/21 In spite of protein milk stools are watery.

10/14/21 Constant loss of weight. One tonsil removed.

10/20/21 Stools still loose with loss of weight. The infant looks very sick.

10/29/21 Swelling and tenderness over right hip. Diagnosis: Osteomyelitis of upper of right femur. Infant is extremely emaciated.

11/ 2/21 Arthrotomy done. Pus obtained. Child very sick. Saline keeps weight horizontal.

11/27/21 Infant very anemic. Transfusion into femoral vein done. Stools normal.

12/ 4/21 Wound over right hip almost closed.

12/21/21 Aphthous stomatitis.

12/25/21 A diarrhea has been present for a few days. Now stools are normal. Weight is going up. Infant looks much better.

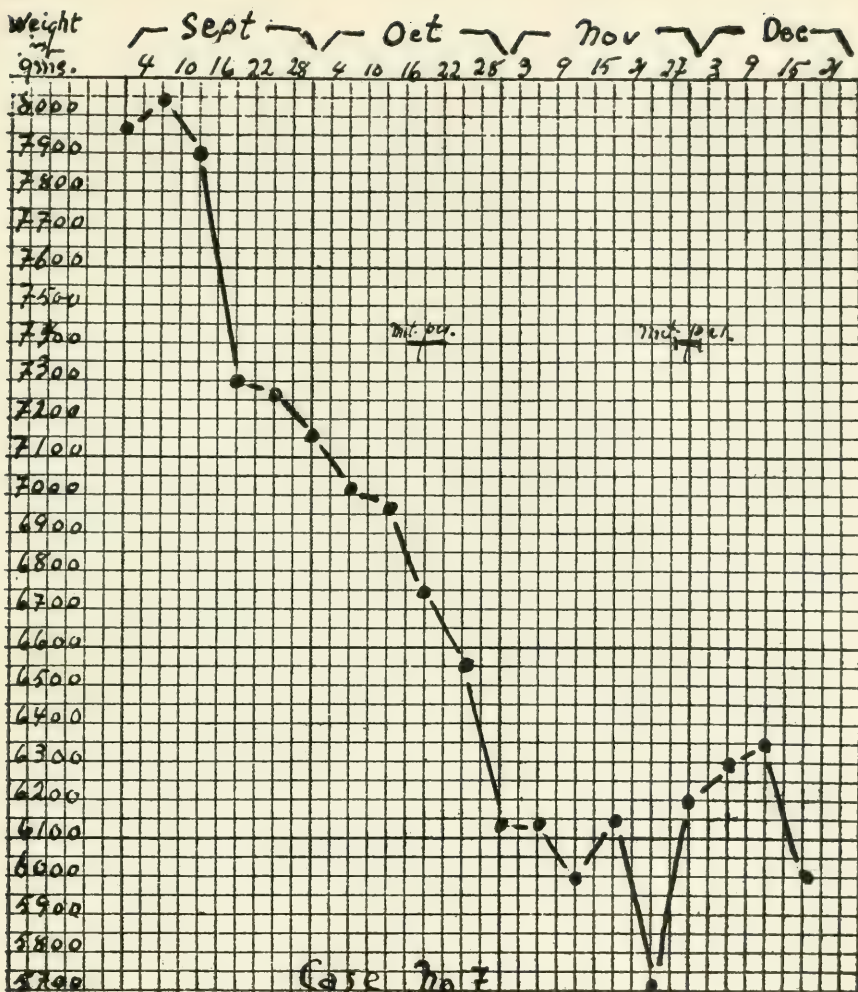
1/24/22 Infant discharged. Weight going up all last month and the infant able to sit up and play. Considerably improved at discharge.

Case No. 8.—4 months male infant. Admitted 9/15/21. Weight 4470 gm.

F. H. — Negative.

P. H. — Has never done well. Born at full term, birth weight unknown. Has been entirely breast fed until two weeks ago. Vomited first weeks of life, often projectile. Was constipated.

P. I. — Started with restlessness two weeks ago when supplementary feeding was given in form of cow's milk. One week ago oatmeal gruel

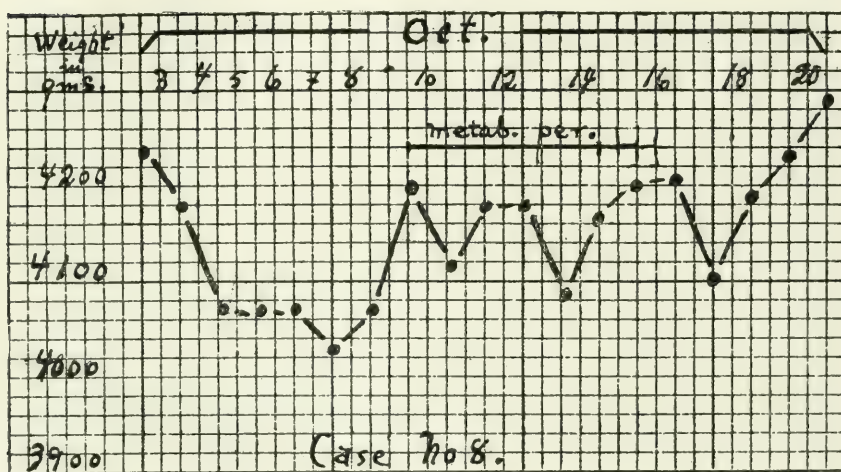


Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
7	6900	12½ mo	w.l.m.	5	wat'y	-125	N.	2.7	2.25	1.58	-1.13	41.5	—
							Cl.	0.33	0.236	0.185	-0.091	44.0	—
							P	0.590	0.233	0.225	+0.132	62	22.3
							CaO	0.835	0.030	0.625	+0.180	25	21.5
							K	0.75	0.297	0.440	+0.013	41.2	1.7
							Na	0.450	0.167	0.380	-0.097	16.0	—
7	6000	14 mo	w.l.m. 900	3	Semif	+20	N	1.40	0.88	0.347	+0.173	75	12.4
							Cl.	0.570	0.375	0.378	-0.183	33.5	—
							P	0.415	0.107	0.230	+0.078	44.5	19.0
							CaO	0.730	0.026	0.510	-0.106	0.	—
							K	0.740	0.330	0.373	+0.037	50.0	5.0
							Na	0.350	0.030	0.463	-0.143	0.	—

was given instead of cow's milk. Infant developed a diarrhea with 5-6 watery greenish stools daily. Has vomited for last two days.

Ph. Ex. — Very poorly nourished and developed infant. Skin shows poor elasticity with very little panniculus. Inguinal glands enlarged. Slight rachitic beading of ribs. Lungs and heart negative. Abdomen: right kidney, edge of liver palpable. Spleen also palpable. Von Pirquet and Wassermann reaction negative. Urine normal.

Course in Hospital. — Stools became normal during course in hospital, but infant would not gain weight. On request patient was discharged 10/26/22. Discharged weight 4200 gm.



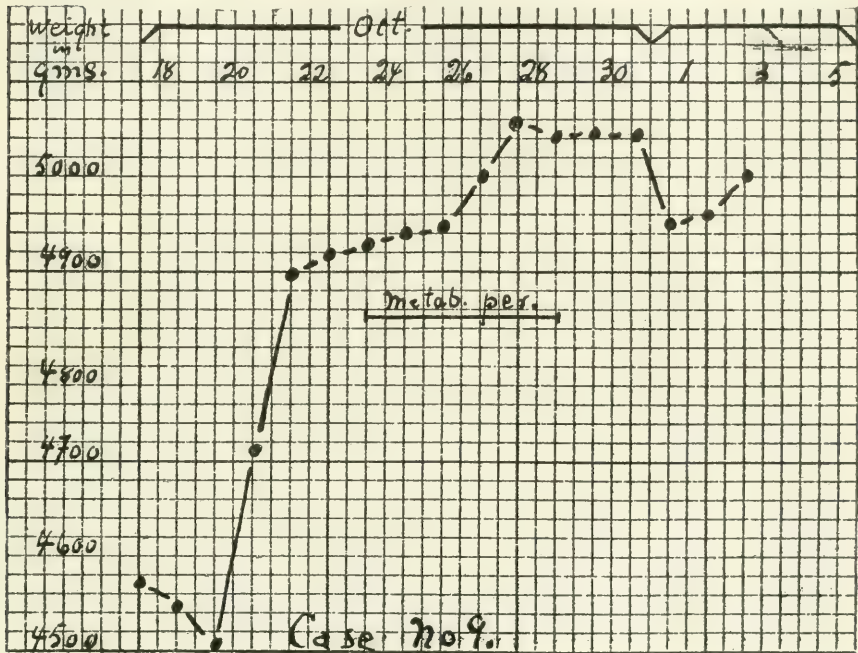
Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
8	4200	4 mos	W. M. 450 Water 270 C. S. 40	5	Soap	—40	N	2.50	1.57	0.318	+0.612	87.3	24.5
							Cl	0.273	0.184	0.015	+0.074	45.0	27.0
							P	0.330	0.138	0.057	+0.135	82.7	41.0
							CaO	0.570	0.016	0.370	+0.184	35.0	32.0
							K	0.370	0.138	0.012	+0.220	96.8	60.0
							Na	0.225	0.102	0.064	+0.059	71.5	26.5

Case No. 9. — 9 months old male infant. Admitted 10/17/21. Weight 4600 gm.

F. H. — Parents low mentality. One brother died from athrepsia.

P. H. — Full term, normal at birth. Breast fed for 2 months. Lost weight on breast. Baby stayed in a hospital for 5 months and improved. When brought back to mother lost weight again. Feeding then unknown.

P. I. — During the last two months baby has lost weight constantly.



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
9	5060	9 mos	W. M. 800 Water 100 CS Cere- al. BD	5	Firm	+104	N Cl P CaO K Na	2.94 0.58 0.52 0.75 0.955 0.305	2.55 0.43 0.218 0.083 0.57 0.273	0.46 0.096 0.144 0.73 0.131 0.075	-0.07 +0.054 +0.158 -0.063 +0.254 -0.043	84.3 83.4 72.5 2.5 86.3 75.5	— 9.3 30.5 — 26.5 —

No vomiting. 2-3 stools daily. Nasal discharge for some time. Has had very poor care in home.

Ph. Ex.—Very small athreptic infant who has the appearance of an old man. Features pinched. Abdomen prominent. No subcutaneous fat present. Skin has an ashy gray color, but is fairly elastic. All superficial glands are enlarged and firm. Liver and spleen not palpable. Rachitic beading of ribs. Impetigo of face, otherwise physical examination negative. Von Pirquet and Wassermann reaction negative. Urine normal.

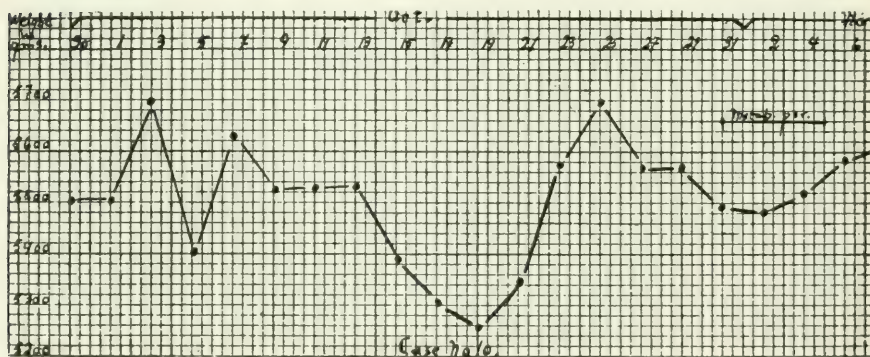
Course in Hospital.—Infant started to gain weight on whole milk cereal feeding. Impetigo cleared up and the patient was discharged considerably improved.

Case No. 10.—10 months male infant. Admitted 9/27/21. Weight 5,400 gm.

F. H.—Negative.

P. H.—Full term, birth weight 7¼ lbs. Has never had breast milk. Has been on Eagle Brand and later various kinds of proprietary infant food have been tried out.

P. I.—2 months ago baby developed diarrhea, with bowel move-



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
10	5500	10 mo	W.M. 1050 Cereal. BD	5	semif	+65	N	5.19	4.65	0.98	-0.44	81.	—
							Cl	0.79	0.56	0.187	+0.043	76.3	5.4
							P	0.70	0.184	0.347	+0.169	50.	24.0
							CaO	1.75	0.035	1.19	+0.525	32.0	30.0
							K	1.27	0.57	0.455	+0.245	64.0	19.3
							Na	0.605	0.345	0.239	+0.021	60.5	3.4

ment every hour. Has been losing weight ever since. For last month infant has had five stools daily. Feeding has been very irregular.

Ph. Ex. — An athreptic male infant with caput quadratum, rachitic beading of ribs, no craniotabes, enlarged inguinal glands. Skin pale, gray, fairly elastic. Very little subcutaneous fat present. Otherwise examination negative. Von Pirquet and Wassermann negative. Urine negative.

Course in Hospital. — During the first six weeks patient would not gain weight. There was no sign of any infection present. Without any essential change in the feeding the infant started to improve and was discharged 3 months after admission in very good condition.

Case No. 11. — Male infant, 5 months of age. Admitted 11/5/21. Weight 5200 gm.

F. H. — Negative.

P. H. — Full term baby. Birth weight 9 lbs. Breast fed two weeks. Was then put on whole milk dilution.

P. I. — Started with vomiting. Was put on barley water by a physician on account of the vomiting and has had very little else than barley water for the past six weeks. The infant is vomiting as soon as milk is given. Stools are fairly good.

Ph. Ex. — Shows an undernourished athreptic male infant. Signs of rickets are present. Inguinal glands enlarged. Otherwise physical examination neg. Von Pirquet and Wassermann reaction negative. Urine negative.

Course in Hospital. — Patient gained weight while in hospital with normal stools and was discharged 9 days after admission. Patient did not vomit while in hospital.

Case No. 12. — Male infant, 2 weeks old. Admitted 12/18/21. Weight 2,400 gm.

P. H. — Full term, birth weight 7 lbs. Normal at birth. Has been breast fed every four hours since birth.

P. I. — Baby will not nurse. Seems very hungry. Sucks fingers most of the time. Losing weight.

Ph. Ex. — Very small and undernourished infant. There is a pustular eruption on cheeks and buttocks. otherwise physical examination is negative. Von Pirquet and Wassermann reaction negative. Urine normal. Mother's breast contained only one ounce by pumping.

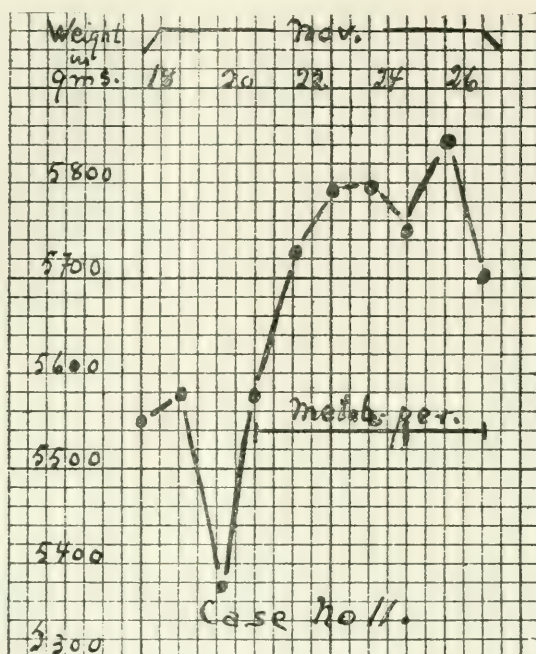
Course in Hospital. — Baby would not gain in spite of breast milk feeding given during whole course in hospital.

2/ 4/22 Both ears bulging, no temperature rise. Paracentesis done—thin pus obtained under pressure.

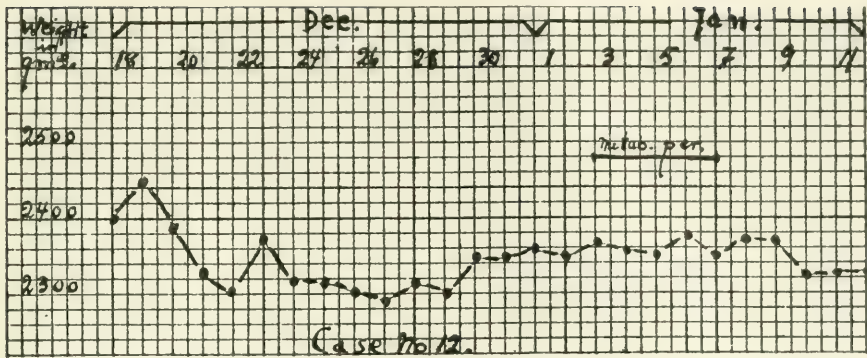
2/10/22 Since paracentesis was done weight has gone up.

2/28/22 Paracentesis had to be repeated several times. Pus obtained at every puncture. No rise in temperature. Weight fluctuating. Discharged 3 months after admission, weight same as on admission.

Case No. 13. — Female infant, 6 months of age. Admitted 10/7/21, weight 2,550 gm.



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
11	5580	5 mos	W. M. 700 B.W. 200 C.S. 30	4	formd	+170	N	3.32	2.53	0.39	+0.40	88.3	12.
							Cl	0.700	0.504	0.096	+0.10	86.3	14.3
							P	0.415	0.205	0.165	+0.045	60.0	10.8
							CaO	1.18	0.04	1.30	-0.16	0	—
							K	1.08	0.413	0.285	+0.382	73.7	35.5
							Na	0.40	0.184	0.134	+0.082	66.5	20.5
11	5750	5 mos	W. M. 700 B.W. 200 C.S. 30 Fat 5.4%	2	wat'y	-50	N	3.05	0.273	0.287	-0.033	90.6	1.08
							Cl	0.545	0.447	0.207	-0.109	62.0	—
							P	0.413	0.198	0.185	+0.030	55.0	7.25
							CaO	1.250	0.016	1.113	+0.121	11.0	9.6
							K	1.05	0.380	0.37	+0.300	65.0	28.5
							Na	0.307	0.307	0.168	-0.168	45.0	—



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
12	2400	4 wks	Br. M. 450	4	Semif.	-10	N	0.600	0.527	0.260	-0.187	56.7	—
							Cl	0.150	0.132	0.004	+0.014	97.3	9.3
							P	0.025	0.031	0.020	-0.026	20.0	—
							CaO	0.150	0.009	0.127	-0.014	15.0	9.3
							K	0.093	0.108	0.033	+0.048	64.5	—
							Na	0.078	0.097	0.038	-0.057	51.0	—

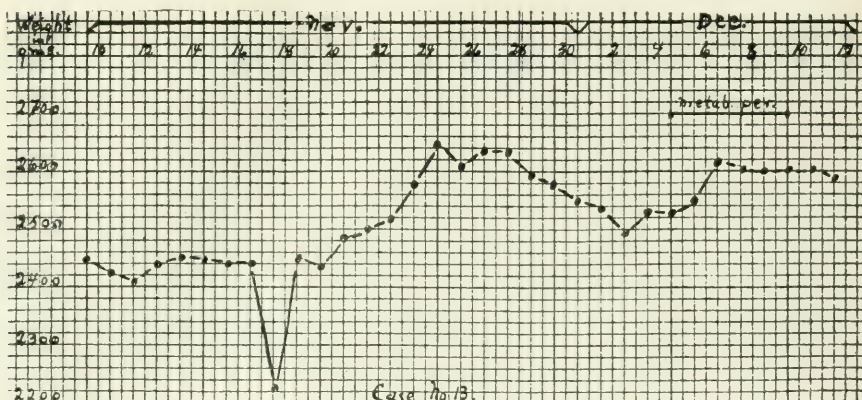
F. H. — Negative.

P. H. — Full term, birth weight 6 lbs. Has never been breast fed, has been on Eagle Brand, Mellin's Food and Malted Milk.

P. I. — Started one month ago with diarrhea. 15-20 stools daily. Loose, yellow with mucous. The infant has vomited every day, often directly after feeding.

Ph. Ex. — An extremely small and malnourished infant with gray, pale dry skin. Inguinal glands enlarged, otherwise no glandular enlargement. Lungs and heart negative. Abdomen much distended with no subcutaneous fat. Liver and spleen not felt. Sputum negative for tuberculosis. Von Pirquet and Wassermann negative. The urine contained few white cells and granular casts.

Course in Hospital. — The infant was fed on whole lactic acid milk and gained weight the first three weeks in hospital. Then she started an irregular temperature with horizontal and falling weight curve with râles in chest. No other signs of parenteral infection except for the pyelitis present. Stools semiformal, two to three daily throughout the whole hospital course. Weight at discharge 2,680 gm.



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
13	2600	6 mos	Br. M. 630	5	Semif	+70	N	1.350	0.340	0.670	+0.340	50.0	25.0
							Cl	0.450	0.245	0.090	+0.115	80.0	25.5
							P	0.173	0.030	0.050	+0.093	71.0	54.0
							CaO	0.740	0.150	0.280	+0.310	62.0	42.0
							K	0.300	0.040	0.160	+0.100	47.0	33.3
							Na	0.174	0.006	0.083	+0.085	52.0	49.0

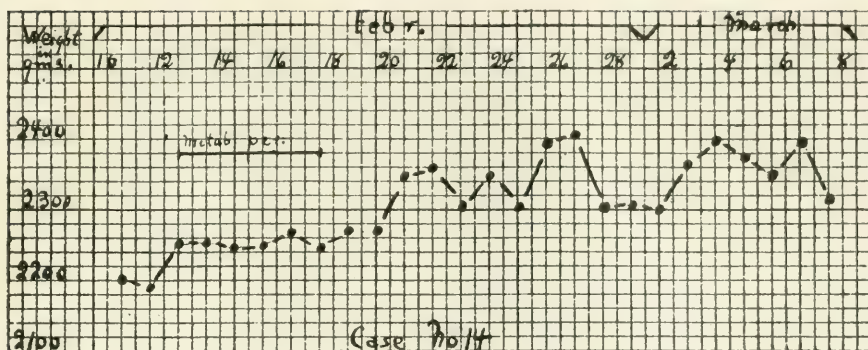
Case No. 14. — Male infant, 5 weeks of age. Admitted 2/10/22. Weight 2,200 gm.

F. H. — Negative.

P. H. — Normal full term, birth weight 7¾ lbs. Breast fed since birth.

P. I. — Was very restless and cried a good deal the first week after birth. Lost weight, was constipated, got more and more quiet and listless. Did not want to take breast. There has been a constant retrogression.

Ph. Ex. — Most extreme malnutrition present. Infant in moribund condition. Lies very quiet. Pulse and respiration slow. No cry. Skin cold, dirty gray, pale and very dry. Mucous membranes red. No general adenopathy. There is a defect in the right parietal bone, otherwise examination negative, except for enlarged inguinal glands. External heat was applied, 200 Cc. of Ringer's solution given intraperitoneally and one-half hour later 50 Cc. 10% glucose was given into the sinus. Immediate improvement was noted. Throughout the hospital course, the infant was first fed on breast milk and later on a whole lactic acid milk. Improvement continued and infant was discharged six weeks after admission.



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
14	2250	5 wks	Br. M. 540	5	Semif	-10	N	0.83	0.425	0.300	+0.105	64.	12.6
							Cl	0.128	0.109	0.003	+0.016	97.6	12.5
							P	0.052	0.016	0.019	+0.017	63.5	32.5
							CaO	0.500	0.059	0.157	+0.284	68.5	57.
							K	0.138	0.039	0.116	-0.017	16.0	—
							Na	0.109	0.045	0.022	+0.042	80.0	38.5

Case No. 15. — Male infant, age 5 weeks. Admitted 2/10/22. Weight 1.770 gm.

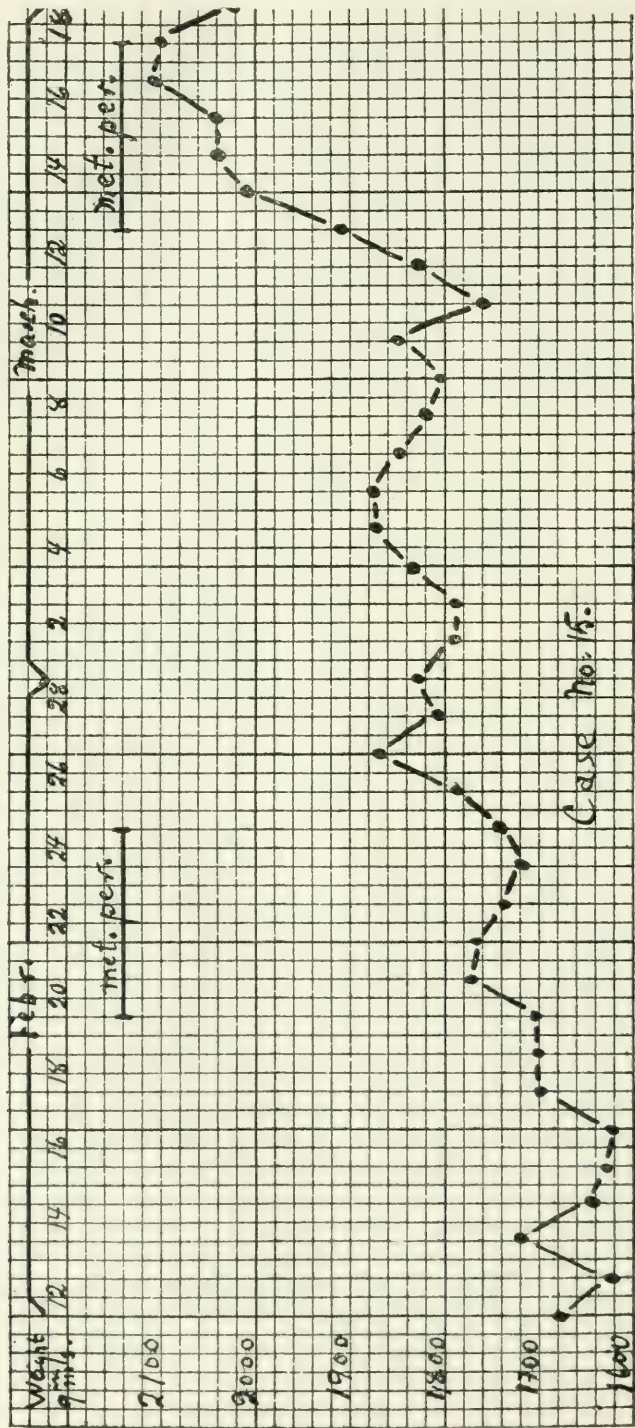
F. H. — Negative.

P. H. — One month premature. Birth weight 6½ lbs. Was breast fed for three to four days, then given Eagle Brand. Infant has had cold in head since birth.

P. I. — Has vomited off and on for last three weeks. The two last days the infant has vomited all feeding given. Two to three stools daily. There has been a constant loss of weight. Infant is always cold.

Ph. Ex. — An extremely emaciated small male infant. Temperature subnormal. Pulse and respiration slow. Very weak cry. Skin pale, gray, cheeks sunken, eyes dull, fontanelle sunken. There is a muco purulent discharge from the nose. There is heard over the heart a loud blowing systolic murmur. Lungs normal, abdomen distended, inguinal glands slightly enlarged.

Course in Hospital. — Patient was given breast milk. Weight was horizontal for one month, feeding then changed to one of whole lactic acid milk, 420cc., Karo Syrup (50%) 120cc., 270 calories per kilo body weight. Infant showed a gain of 300 gm. on this feeding. For the last 14 days he was running a temperature with bronchitis and otitis media. Patient still in hospital.



Number	Weight in Grams	Age	Feeding	Number of E.A.D. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
15	1700	5 wks	B.M. 540	5	Semif	+40	N	0.82	0.315	0.161	+0.344	80.3	42
							Cl	0.107	0.047	0.011	+0.049	90.0	46
							P	0.067	0.009	0.014	+0.044	79.0	66
							CaO	0.320	0.026	0.147	+0.147	54.0	46
							K	0.143	0.033	0.042	+0.068	71.0	48
							Na	0.064	0.019	0.005	+0.040	92.0	63
15	1910	8 wks	w.l.m. 420 K.S. 120	5	Loose	+190	N	1.67	0.165	0.56	+0.945	66.5	57
							Cl	0.535	0.071	0.101	+0.363	81.0	68
							CaO	1.09	0.019	0.500	+0.571	54.0	52.5
							K a	0.42	0.055	0.144	+0.221	66.0	52.5
							N	0.41	0.062	0.145	+0.203	65.0	50.0

Case No. 16.—Female infant, age 3 weeks. Admitted 12/7/21, weight 2,100 gm.

F. H. — Parents low mentality.

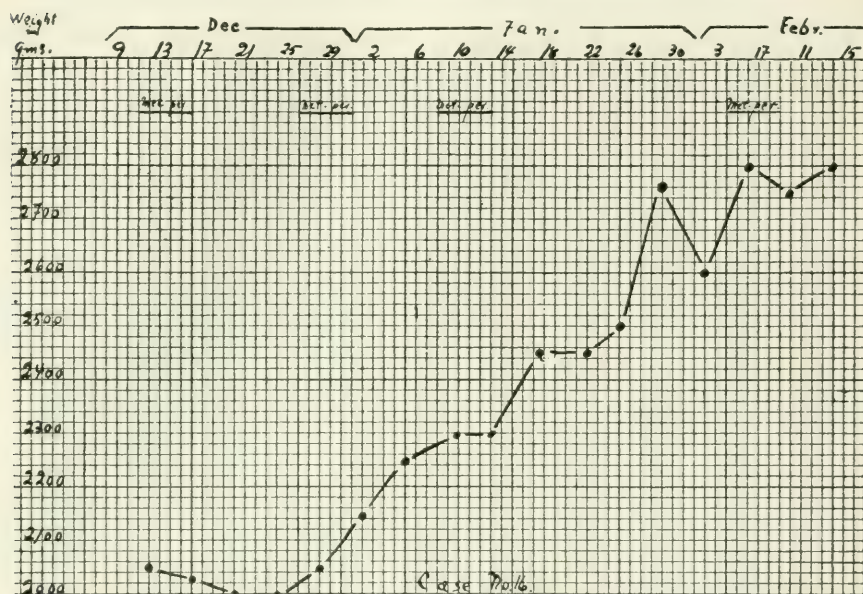
P. H. — One month premature, birth weight 2,000 gm. Fed on breast milk for a few days then on cow's milk formula. No fever, no vomiting, no diarrhea.

P. I. — Failure to gain weight without any acute symptoms.

Ph. Ex. — Patient very poorly developed and nourished infant. Skin dry, gray with peeling epidermis. Inguinal glands slightly enlarged, but otherwise no glandular enlargement is noted. Fontanelle is wide open. Lungs, heart, abdomen negative. Liver and spleen not felt. Von Pirquet and Wassermann reaction negative. Urine negative.

Course in Hospital. — Weight horizontal for first three weeks in spite of continuous feeding with breast milk. Infant was transfused 12/26/21. Since that date weight began to go up and continued so for three weeks. Weight was stationary for another week. Transfusion No. 2 was done and after this baby gained weight again. The infant then developed an otitis media without rise in temperature and after several paracenteses the infant improved greatly and was discharged in good condition weighing 3,230 gm.

892 ADVANCED CHRONIC NUTRITIONAL DISTURBANCES IN INFANCY



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
16	2030	3 wks	B. M. 450	5	Semif	+40	N	0.97	0.367	0.480	+0.123	50.5	12.7
							Cl	0.225	0.098	0.035	+0.092	84.5	40.5
							P	0.054	0.029	0.032	-0.007	41.4	—
							CaO	0.280	0.026	0.225	+0.029	20.0	10.4
							K	0.263	0.060	0.177	+0.026	33.0	9.9
							Na	0.124	0.004	0.043	+0.077	65.5	62.0
							N	0.94	0.423	0.202	+0.315	78.5	33.5
16	2050	5 wks	L.B.M Br. M.	3	Form.	+50	Cl	0.151	0.150	0.020	-0.019	86.7	—
							P	0.043	0.012	0.016	+0.015	63.0	35.0
							CaO	0.274	0.015	0.157	+0.102	43.0	37.0
							K	0.265	0.020	0.042	+0.203	84.0	76.5
							Na	0.119	0.001	0.046	+0.072	61.0	60.0
							N	1.21	0.192	0.240	+0.778	80.0	64.0
							Cl	0.210	0.136	0.025	+0.049	88.0	23.5
16	2270	7 wks	L.B.M B.M.	5	Semif	+25	P	0.057	0.020	0.018	+0.019	68.5	33.0
							CaO	0.510	0.017	0.227	+0.266	55.0	52.0
							K	0.180	0.053	0.061	+0.066	66.0	36.5
							Na	0.130	0.034	0.035	+0.061	73.0	47.0
							N	1.480	0.710	0.300	+0.470	79.7	31.8
							Cl	0.440	0.350	0.021	+0.067	95.0	15.2
							P	0.250	0.112	0.074	+0.064	70.0	25.5
16	2800	11 wks	L.B.M B.M. WLM	4	Semif	+4	CaO	1.17	0.161	0.950	+0.059	19.0	50.5
							K	0.465	0.235	0.200	+0.030	57.0	6.5
							Na	0.355	0.175	0.136	+0.044	62.0	12.4

Case No. 17. — Male infant, age 5 weeks. Admitted 1/14/22, weight 2,800 gm.

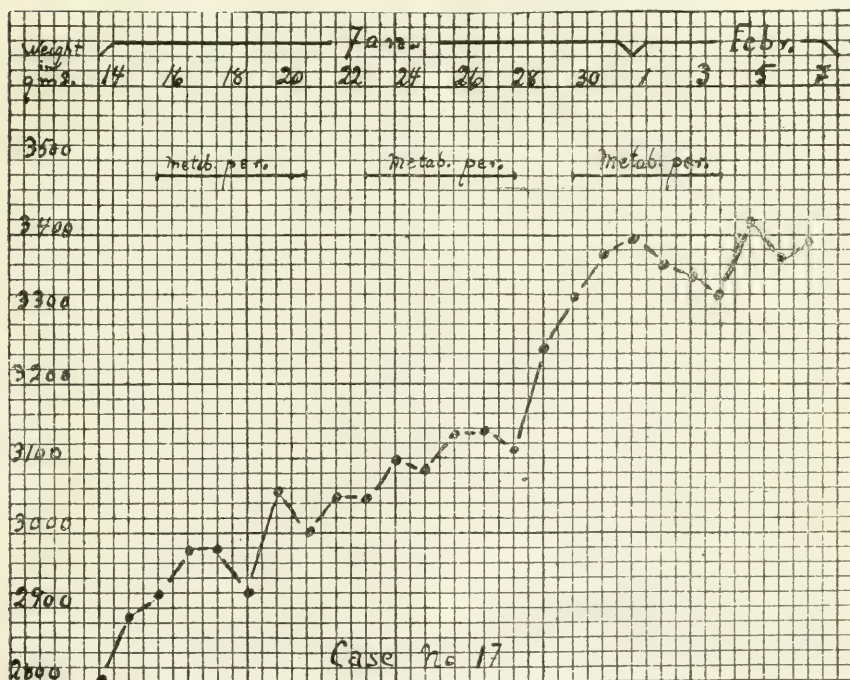
F. H. — Negative.

P. H. — Birth weight $8\frac{1}{4}$ lbs. Full term normal infant. Breast fed three months then fed on Eagle Brand.

P. I. — Baby vomits frequently and has not gained since birth. For the last 3 weeks infant has lost weight, stools have been normal.

Ph. Ex. — An undernourished male infant, enlarged inguinal glands, otherwise no glandular enlargement. Skin dry and desquamating over the trunk. Lungs, heart, abdomen negative. Von Pirquet and Wassermann reaction negative. Urine negative.

Course in Hospital. — Infant had an attack of cyanosis three days after admission. No heart murmur was heard. Otherwise the infant did very well in the hospital and was discharged in a very good condition.



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
17	2,920	5 wk.	WLM. 480 Water 180 K.S. 60 1.6% fat.	5	Loose	+80	N.	1.610	0.600	0.600	+0.410	62.7	25.5
							Cl.	0.600	0.310	0.040	+0.250	94.0	41.5
							P.	0.233	0.110	0.066	+0.057	71.5	24.5
							CaO.	0.840	0.015	0.690	+0.135	18.0	16.0
							K.	0.620	0.220	0.220	+0.180	64.5	29.0
							Na.	0.380	0.098	0.120	+0.162	68.5	42.5
17	3,050	6 wk.	3.6% fat.	5	Firm	+60	N.	2.180	0.805	0.213	+1.162	90.2	53.5
							Cl.	0.485	0.360	0.009	+0.116	98.1	24.0
							P.	0.250	0.150	0.058	+0.042	77.0	16.8
							CaO.	0.880	0.040	0.770	+0.070	13.0	7.9
							K.	0.670	0.410	0.091	+0.169	86.4	25.0
							Na.	0.250	0.130	0.024	+0.096	90.4	38.5
17	3,320	6 wk.	4.8-5.2% fat.	5	Firm	+10	N.	2.450	0.990	0.277	+1.183	88.7	48.7
							Cl.	0.660	0.375	0.017	+0.268	97.4	40.5
							P.	0.255	0.150	0.050	+0.055	80.0	21.5
							CaO.	0.880	0.087	0.780	+0.013	12.0	1.5
							K.	0.630	0.380	0.120	+0.130	81.0	20.5
							Na.	0.395	0.360	0.015	+0.020	96.2	5.0

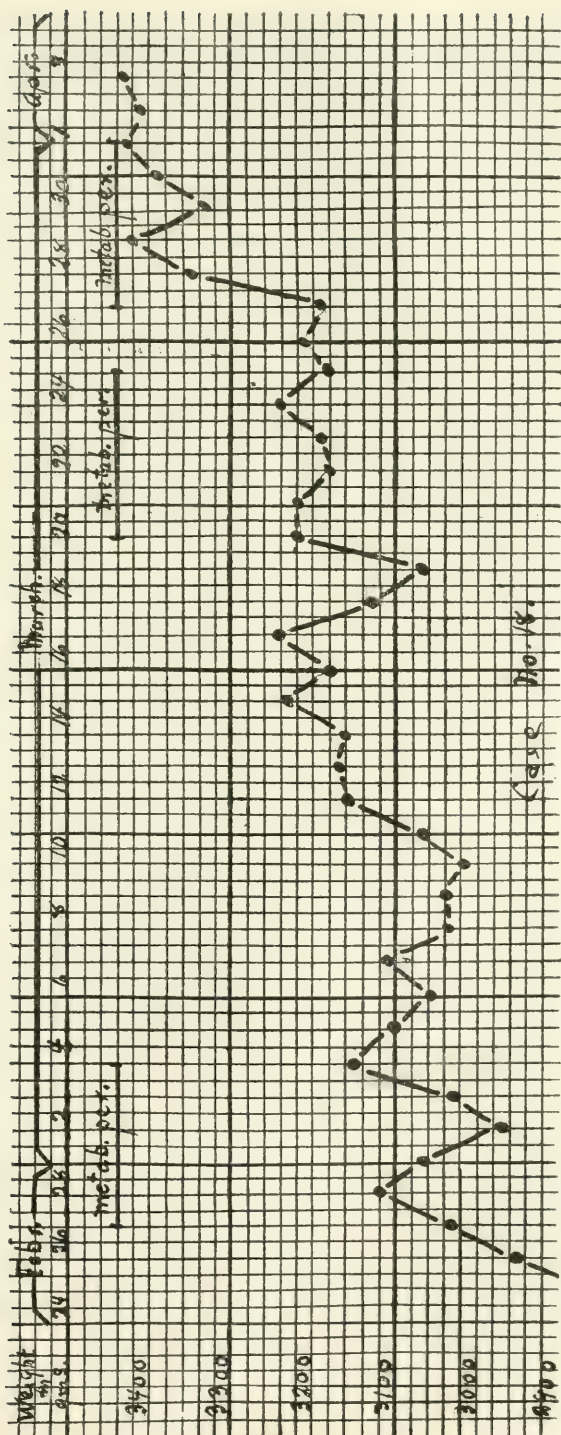
Case No. 18.—Male infant, age 2 months. Admitted 1/14/22. Weight 2700 gm.

F. H.—Negative. One of twins.

P. H.—Full term infant, birth weight 5 lbs. Normal at birth. Breast fed every one and one-half hours. There has been no gain in weight.

P. I.—Started five days ago when supplementary feeding in the form of Eagle Brand was given. Patient vomited all of the feeding and has during the last few days refused to take any food. No diarrhea. Infant has lost weight for the last three weeks.

Ph. Ex.—Very poorly nourished infant, slightly enlarged inguinal glands. Otherwise no glandular enlargement. Skin has fair elasticity but there is only a small amount of subcutaneous tissue. Throat, ears,



lungs, heart, abdomen neg. Von Pirquet and Wassermann reaction negative. Urine negative.

Course in Hospital. — Infant fed on breast milk but weight was falling and the general condition was extremely poor.

2/19/22 Without showing any rise in temperature left ear drum became red and bulging. On paracentesis there was free flow of pus and since that date weight has been increasing.

3/ 5/22 Infant developed bronchitis with horizontal weight and rise in temperature. After temperature returned to normal weight curve started to go up.

4/ 6/22 Infant is still in hospital and is now in a very good condition. Weight 3,620 gm.

Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
18	3030	3 mos.	WL M 570 K S 120	5	Wat'y	+120	N	2.450	0.560	0.327	+1.563	86.6	64.0
							Cl	0.420	0.250	0.050	+0.090	81.0	21.5
							P	0.162	0.022	0.070	+0.070	57.0	43.0
							CaO	0.860	0.010	0.680	+0.170	21.0	20.0
							K	0.640	0.200	0.174	+0.266	73.0	41.5
18	3220	4 mos.	Br. M. 480	5	Loose	-40	Na	0.465	0.092	0.173	+0.200	63.0	43.0
							N	2.100	0.515	0.430	+0.155	79.5	55.0
							Cl	0.230	0.030	0.008	+0.192	96.6	84.0
							P	0.088	0.046	0.037	+0.005	58.0	5.7
							CaO	0.598	0.012	0.312	+0.271	47.5	46.0
18	3290	4 mos.	W. M. 840 C. S. 30	5	Locse	+230	K	0.248	0.070	0.127	+0.051	49.0	20.5
							Na	0.200	0.024	0.071	+0.105	64.5	52.5
							N	3.600	0.940	0.600	+2.060	83.0	57.0
							Cl	0.730	0.002	0.290	+0.438	60.5	60.0
							P	0.225	0.032	0.073	+0.120	67.5	53.5
							CaO	1.380	0.011	0.880	+0.480	36.0	35.0
							K	0.550	0.069	0.340	+0.141	38.0	25.5
							Na	0.430	0.009	0.150	+0.271	65.0	63.0

Case No. 19. — Male infant, 3 months of age. Admitted 11/11/21. Weight 5,100 gm.

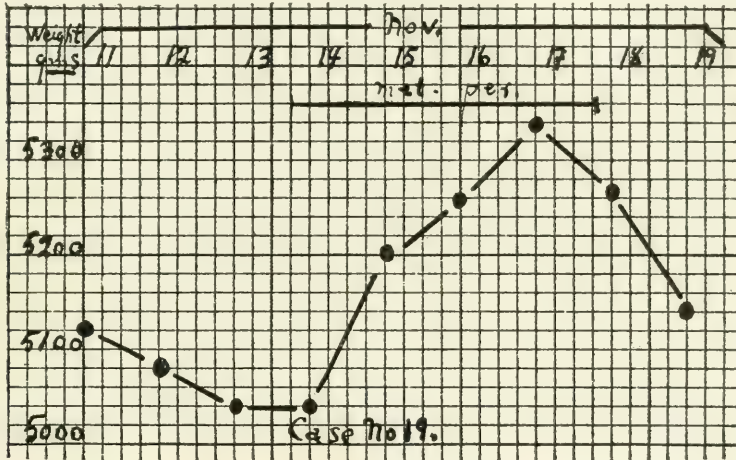
F. H. — Negative.

P. H. — Full term. Birth weight 9 lbs. Breast fed one month. Has since then been on artificial feeding.

P. I. — Started four days ago with loose stools, no mucous and no blood noticed in stools.

Ph. Ex. — Very well nourished infant with good elasticity of skin. No eruptions. Child does not look sick. No glandular enlargement. Throat, lungs, heart, abdomen negative. Stools semiformed.

Course in Hospital. — Infant was fed on whole lactic acid milk. The stools were perfectly normal the day after admission and remained so during the whole course in hospital. This infant was considered a normal infant, and the total metabolism study was done in order to have a normal case to compare with the athreptic ones.



Number	Weight in Grams	Age	Feeding	Number of Exp. days	Consistency of stools.	Loss or Gain, in Grams.	Constituents examined	Average Intake in 24 hours	Average Excretion Urine in 24 hours.	Average Excretion Stools in 24 hours.	Balance.	Percentage absorption.	Percentage retention.
19	5,100	3 mo.	WLM. 600 Water 250 K.S. 50	4	Semif	+230	N.	3.400	1.780	0.590	+1.030	83.0	30.3
							Cl.	0.680	0.180	0.120	+0.380	82.0	56.0
							P.	0.490	0.200	0.110	+0.180	78.0	36.7
							CaO.	1.390	0.018	0.770	+0.600	44.0	43.0
							K.	1.140	0.530	0.210	+0.400	82.0	35.0
							Na.	0.240	0.100	0.065	+0.075	73.0	31.0

TABLE XXXIII.
*Percentage Absorption and Retention of Nitrogen and Salts
in Athreptic Infants.*

No.	No. of Exp. days	Loss or Gain Gm.	% Absorp.	% Retent.	% Absorp.	% Retent.	% Absorp.	% Retent.	% Absorp.	% Retent.
1	1	—	40	neg.	45.5	neg.	0	neg.	0	neg.
1	1	+ 50	83.3	33.5	44.0	neg.	25.0	21.5	41.2	1.7
2	2	+ 100	71.0	neg.	33.5	neg.	0	neg.	50.0	5.0
2	5	+ 250	79.0	34.0	45.0	neg.	35.0	32.0	96.3	60.0
3	4	+ 100	77.0	36.5	82.7	41.0	2.5	neg.	86.3	26.5
3	4	+ 60	74.7	51.0	83.4	9.3	32.0	30.0	64.0	19.3
4	4	+ 20	75.0	17.5	76.3	5.4	0	neg.	73.7	35.5
4	4	+ 80	72.0	31.0	86.3	14.3	0	neg.	65.0	28.5
4	4	+ 130	80.6	34.7	62.0	7.25	11.0	9.6	65.0	45.0
5	6	—	60.0	neg.	62.0	neg.	15.0	9.3	64.5	51.0
6	5	— 5	41.5	neg.	44.5	neg.	62.0	42.0	47.0	neg.
7	3	+ 20	75.0	12.4	33.5	neg.	0	neg.	50.0	33.3
7	7	+ 20	87.3	24.5	45.0	27.0	35.0	32.0	96.3	80.0
8	5	—	40	84.3	83.4	9.3	2.5	neg.	86.3	neg.
9	5	+ 104	81.0	neg.	76.3	5.4	32.0	30.0	64.0	63.0
10	5	+ 65	88.3	12.0	86.3	14.3	0	neg.	73.7	52.5
11	4	+ 170	90.6	1.08	62.0	neg.	11.0	9.6	65.0	60.0
11	2	—	50	90.6	97.3	neg.	15.0	9.3	64.5	51.0
12	4	—	10	56.7	97.3	9.3	15.0	9.3	64.5	neg.
13	5	+ 70	50.0	25.0	80.0	25.5	62.0	42.0	47.0	49.0
14	5	+ 10	64.0	12.6	97.6	12.5	68.5	57.0	16.0	38.5
15	5	+ 40	80.3	42.0	90.0	46.0	54.0	46.0	71.0	92.0
15	5	+ 190	66.5	81.0	81.0	68.0	54.0	52.5	66.0	60.0
16	5	+ 50	50.5	57.0	84.4	40.5	20.0	10.4	33.0	65.5
16	3	+ 50	78.5	12.7	86.7	neg.	20.0	10.4	33.0	9.9
16	5	+ 25	80.0	33.5	86.7	neg.	43.0	37.0	84.0	76.5
16	5	+ 40	62.7	31.8	88.0	23.5	55.0	52.0	66.0	36.5
16	5	+ 80	79.7	35.8	95.0	15.2	19.0	50.0	57.0	6.5
17	5	+ 4	62.7	94.0	41.5	71.5	18.0	16.0	64.5	29.0
17	5	+ 60	90.2	53.5	98.1	24.0	13.0	7.9	86.4	68.5
17	5	+ 10	88.7	48.7	97.4	40.5	12.0	1.5	81.0	20.5
17	5	+ 120	86.6	64.0	81.0	21.5	21.0	20.0	73.0	41.5
18	5	—	79.5	55.0	96.6	84.0	47.5	46.0	49.0	20.5
18	5	+ 40	79.5	55.0	96.6	84.0	47.5	46.0	49.0	25.5
18	5	+ 230	83.0	57.0	60.0	60.0	36.0	35.0	38.0	63.0

In the group of infants examined there are included two who were not born at full term (No. 15 and 16). Both infants presented a typical picture of athrepsia. In two cases (No. 11 and 17) the effect of fat increase in the diet was observed. The results are summarized in Table XXXIII.

In order to be able to compare my figures with figures obtained on normal infants a table of the findings on normal breast fed infants from the literature is recorded. (Table XXXIV.).

From the results it will be seen that of the eighteen athreptic infants examined over several five day periods, seven of these (39%) showed a negative nitrogen balance. These infants have not shown a particular fall in weight. Only one infant (No. 7) showed a rapid loss of weight. In the case of the others the weight curve during the experimental period was either horizontal or increasing. On referring again to the figures it is seen that the retention of sodium, chloride and calcium follow rather closely the nitrogen retention. Where the nitrogen balance is negative or low the salts mentioned show a corresponding negative or low balance except for calcium in Nos. 2, 3 and 10. The retention of phosphorus and potassium is good in most instances. The absorption seems to be about normal for all salt constituents except calcium. Nitrogen absorption is essentially normal.

It has generally been believed that the nitrogen retention is little effected, if at all, by the trend of the weight curve. According to my results, such is not the case. Even with increasing weight, the nitrogen balance may be negative, for example, Cases No. 2 and No. 9.

Why my results differ from those of other investigators is difficult to tell. A larger number of total metabolism experiments on athreptic infants have been made, in the course of this study, than have been made by previous workers combined. Another point which should also be mentioned is that all nitrogen determinations were done on fresh moist stools directly after collection of the specimens was complete. During each day the specimens were carefully preserved with toluol and kept in the ice box until the 24 hours were up. Each day's specimens were examined separately. Earlier investigators, as far as I have been able to find, have made nitrogen determinations on dried feces and usually on all specimens collected for the whole experimental period. A loss of nitrogen necessarily takes place under these conditions. Gamble¹⁴¹ has stated that as much as 20 per cent. of the nitrogen may be lost in this way. Whether this difference in the technic will explain the variations in results is difficult to state, but my findings seem to point to a deficiency in the nitrogen metabolism of these infants. From the figures it may be seen that the nitrogen absorption is fairly normal. The average for 30 different periods was 73.8 per cent. We obviously, then, have to consider the poor nitrogen retention as not due to a lack of absorption, but due to a deficient utilization throughout the organism, or to actual destruction of the body tissues. This may be considered as a result of the above mentioned low circulation with diminished blood volume. As a further result there may be an increased excretion of certain products of the

TABLE XXXIV.

Nitrogen and Salt Retention and Absorption in Normal Infants, According to Earlier Literature

Author's Name	Age.	Feeding	Weight Gain	N.		Na Cl.		P ₂ O ₅		CaO		K ₂ O		Na ₂ O		
				Absorp.	Retent.	Absorp.	Retent.	Absorp.	Retent.	Absorp.	Retent.	Absorp.	Retent.	Absorp.	Retent.	
Lindberg I...	2½ mos.	B.M.	4,285	10	78.01	39.22	94.9	34.86	81.17	65.39	28.97	21.86	80.65	17.57	75.87	63.28
Lindberg II...	2½ "	B.M.	4,370	23	80.41	38.08	90.45	34.29	78.62	48.34	33.15	24.43	75.61	27.8	71.55	45.55
Blauberger.....	5 "	B.M.	6,740	10			93.1	88.00	89.17	49.9	75.8	64.5	87.44	39.8	9.36	—
Tobler-Noll...	5 "	B.M.	4,000	24.3	88.4	48.9	95.98	15.34	83.68	56.51	37.8	22.3	83.04	50.27	96.17	92.64
Klatz-2	5 "	B.M.	3,420	3.3			67.25	42.05	69.68	30.24	40.43	32.19	74.24	59.81	67.25	42.05
Michel Perret	3 "	B.M.	4,726	29	89.5	46.9	96.3	24.8	73.20	61.70	47.5	39.5				
Peiser Gl.....	2 "	B.M.	3,720	36	82.2	44.23					24.4	17.07				
Peiser Band...	1½ mo.	B.M.	3,880	30	70.8	46.07										
Schabad	4 mos.	B.M.	7,700	—					79.2	53.5						
Keller IV.....	2 "	B.M.	4,350	28	87.0	45.0			84.4	54.1						
Keller VIII...	2½ "	B.M.	4,380	10	95.2	30.5										
Klatz I.....	6 "	Artif.														
		Fed.	4,200	0	87.7	26.6			63.6	31.7	30.5	26.4	87.4	23.1	93.7	26.1
Klatz II.....	7 "	Artif.														
		Fed.	6,620	—80	91.7	3.3			78.4	30.0	7.4	6.9	85.4	29.0	86.0	24.4
Uthelm.....	3 "	Artif.														
		Fed.	5,100	+230	83.0	30.3	82.0	56.0	78.0	36.7	44.0	43.0	82.0	35.0	70.5	31.0

Klatz I. Fed on equal parts of milk and cereal soup.

Klatz II. Fed on equal parts of skimmed milk and cereal soup.

Uthelm Fed on whole lactic acid milk 600, water 250, Karo syrup 50% 50.

intermediary metabolism which would normally have been broken down in the body, constituents as the organic acids mentioned above.

If the foregoing assumptions are correct, one would be required to assume a definite lowering of the metabolism in these infants. Measurements of the total respiratory exchange show an increased metabolism when calculated in relation of calories to body weight. This higher metabolism has been considered the result of a relatively increased surface area, partly due to the small body, and partly to the loss of subcutaneous fat. If, however, the calories are calculated, not in relation to the actual weight of the infant, but to the expected weight, that is to say, the weight as it would be if the subcutaneous fat were restored to the body, it is found that the metabolism of very athreptic infants is then below that of normal infants (Talbot¹⁴²). Fleming¹⁴³ also finds an almost identical state of affairs. At 65% of the expected weight, the heat output falls below 47 calories per kilo of expected weight, according to age, and gradually decreases as atrophy advances. Above 65% it remains fairly constant, between 47 and 60 calories per kilo of expected weight. This finding seems to indicate that the active tissues of the body are not functioning to a normal extent. In other words, the metabolism of these infants is inefficient. According to this the negative salt balance could be considered as the result of the lowered metabolism with the deficient nitrogen utilization.

These findings give no support to the conception that a demineralization process is the primary factor in the pathogenesis of athrepsia.

It will be noted from the figures that the calcium absorption and retention is low in most of my cases. According to Holt, Courtney and Fales¹⁴⁴ the percentage absorption of calcium in eighteen healthy children were from 35% to 55% of the intake. In healthy breast fed infants the absorption higher, 66.7%. Compare otherwise earlier author's results in Table XXXIII. Most of my cases show a considerably lower calcium absorption. This finding points in the direction of a pathological bone formation in these infants, and will be mentioned later in connection with the blood salts.

The main idea in Czerny-Keller's theory of athrepsia is that an increased loss of alkali due to the presence of fatty acids in the intestinal tract takes place by way of the bowel. This results in an increased ammonia coefficient in the urine, which according to Czerny is due to a relative acidosis. As stated above, the ammonia coefficient was determined in three of our cases during an increased fat intake, but no influence on the ammonia output was observed. The organic acids in the urine also remained unchanged. An extensive literature has developed on the influence of fats on the excretion of salts. The earlier findings of Steinitz have not always been confirmed. My own experiments on the influence of fat in the diet on salt metabolism were made on a two months old athreptic infant who was fed during the first week on 1.6 per cent. fat (11.5 gm. daily) during the second week on 3.5 per cent. fat (25.2 gm. daily) and during the third week for 2 days

on 4.8 (34.6 gm.) for 3 days on 5.2 per cent., fat, (37.4 gm. daily.) (No. 17. on page.....)

As can be seen from case No. 17, the excretion of potassium and sodium is increased in the urine during the high fat feeding, and decreased in the stools. This is just opposite of what should be expected, according to Czerny. The chloride excretion and absorption was unchanged. The phosphorus output was slightly increased in the urine. The calcium metabolism however seems to have been influenced by the amount of fat in the feeding. There is an increased output in the stools with a fall of absorption from 18 per cent. to 13 per cent. subsequently to 12 per cent. The fall in retention was from 16 per cent. to 7.9 per cent. and 1.5 per cent. The nitrogen retention shows a definite increase. A single case is naturally quite insufficient from which to draw any definite conclusion.

(d) Methods Used in Total Metabolism Experiments.

Nitrogen has been determined according to Kjeldahl. For fat determination Clausen's method has been used (to be published). The principle of this method is: After saponification with alkali the fatty acids are liberated with sulfuric acid, extracted with ether and titrated in alcoholic solution with alcoholic sodium hydroxide. Benedict's method¹⁴⁴ has been used for determining sugar in milk. Stools have been hydrolyzed and the sugar determined according to Schaffer and Hartman's method¹⁴⁵. Chlorides have been determined as sodium chloride according to Rusznyak¹⁴⁶. The calculated chloride is put down in the tables. Phosphorus has been determined according to Bell and Doisy¹⁴⁷; Calcium according to McCrudden¹⁴⁸. Potassium and sodium have been determined according to Kramer¹⁴⁹ as chlorides after ashing until constant weight. Potassium has then been precipitated and titrated as potassium sodium cobalt nitrite and sodium determined indirectly.

13. Blood Salts in Athrepsia.

If the demineralization process is an essential feature in the pathogenesis of athrepsia, we ought to see some constant changes in the composition of the mineral salts of the blood. It has not been possible to find any references to earlier work on the different salts in the blood in cases of athrepsia. Salge⁵⁰ studied the blood of two athreptic infants. He found the freezing points and the electrical conductivity very low, and drew the conclusion that there must be a decreased osmotic pressure on account of loss of mineral salts. In both infants the protein, as determined by the refractometric method, was also low. My own determinations appear in Table XXXV.

TABLE XXXV.

*Blood Salts in Infants, Expressed as Mg. per 100 Cc.
Blood Serum.*

No.	Age.	Diagnosis	Cl. as NaCl.	Na.	K.	Ca.	Inorg. P.	Inorg. S.	% protein
1	5 wk.	Athrepsia	635	265		12.	3.1		5.25
2	3 mo.	Athrepsia	615	247		10.9	2.22	4.2	4.81
2	3 "	Athrepsia	615	270	18.2	7.8	3.56	0.9	5.03
3	3 "	Athrepsia	485		28.4				5.47
4	6 "	Athrepsia	548	234	17.8	9.8	2.07	0.3	6.55
5	5 wk.	Athrepsia	550	274			2.20		5.78
6	5 "	Athrepsia	542	247		11.1	3.2	0.76	5.90
7	5 "	Athrepsia	677	270		13.0	3.85		4.81
8	12 mo.	Athrepsia	525	297					5.80
9	6 "	Athrepsia	562	310	28.4	10.0		3.2	6.98
10	6 wk.	Athrepsia	585	197		11.2	3.06	0.4	6.55
11	4 mo.	Athrepsia	660	270		11.6			6.98
12	12 yr.	Normal	610	315	28.5	10.4		1.00	8.80
13	9 "	Normal	570	280		11.4	4.04	1.14	9.77
14	9 "	Normal	585	323	21.3	11.4	4.15	1.25	9.13
15	9 mo.	Normal	515	346	21.3	11.2	6.25	0.40	6.98
16	9 "	Rickets	519	352	17.7				6.77
17	14 "	Birth Hemorrhage	570	324					
18	2 "	Hypothrepsia	760	301		7.00	5.0	0.98	5.90
19	1 "	Pyloric Stenosis	515	279		10.0	4.4		6.77
20		Non-diabetic acidosis	645	274					6.77
21	4 "	Anemia Noma.	510	234	26.2	10.0		1.78	6.98
22	5 mo.	Pneumonia	670	346	21.0				6.12
23	13 "	Tbc. Meningitis	455	265	26.0	9.0		2.0	6.6 7.4

The blood of twenty-three patients has been examined. Eleven samples from athreptic infants, and twelve from other patients in the hospital. All examinations were done on clear blood serum immediately after collection. (For technic see "Methods"). A complete salt determination was not possible on any one blood on account of the rather large amount of blood necessary for this, but determinations have been done on different salts in individual cases so that an impression may be gotten by comparing the figures with the normal. Sodium, Chloride and also protein was determined in nearly all cases.

It is seen from Table XXXV. that while chlorides are present in a normal amount in nearly all cases, the sodium content of athreptic infants' blood seems to be lower than normal. Taking Kramer's¹⁵⁰ figures of 280 to 310 mg. sodium per 100 cc. blood serum as normal, we find that most of my figures for athreptic infants lie below this normal limit, while my figures for normal, correspond fairly well with those of Kramer. The lowering of the sodium content was not marked but occurred in all but three cases. We know that normally some of the sodium ion is combined with protein, which acts as a weak acid radical, and if the protein concentration were lowered the sodium con-

tent should be correspondingly decreased. It is seen from the table that, in general, the low sodium in the blood is accompanied by a low protein concentration. This may well be the explanation of the low sodium figures.

Potassium, calcium and the sulphates do not show any characteristic changes.

The inorganic phosphorus figures seem to be below the average normal findings. According to Iversen and Lenstrup¹⁵¹ the average normal inorganic phosphorus content of the serum of breast fed infants is 6.6 mg. per 100 cc. The average for artificially fed infants is 4.4 mg. According to Howland and Kramer¹⁵² the normal figure is 5 mg. All of these authors emphasize that a low phosphorus content of the blood is characteristic of rickets. Iversen and Lenstrup found as an average figure for rachitic infants 3.3 mg., which after treatment rose to about 5.5 mg. Howland and Kramer¹⁵² state that all children under two and one-half years of age, in whom they found an inorganic phosphorus content of the blood, were suffering from active rickets.

It may be that the low phosphorus content in these infants' blood serum means that in spite of the young age a rachitic process is starting. On taking this finding, together with the somewhat impaired calcium metabolism shown in the same infants, it would seem probable that bone formation was proceeding in a faulty manner. Schiff¹⁵³ has emphasized the fact that there very seldom is clinical rickets present in athreptic infants, but he nevertheless thinks that a rachitic process is going on in the organism of the majority of athreptic infants. This assumption has been confirmed at autopsy. X-Ray pictures were taken of the bones of some of those infants with low calcium retention and low phosphorus content of the blood but no characteristic rachitic changes were found in any case, except No. 4, an infant 6 months old.

METHODS.

Chlorides determined according to Rusznyak¹⁴⁶. Sodium according to Kramer¹⁵⁴; Potassium according to Kramer¹⁴⁹; Calcium according to Kramer¹⁵⁵. Inorganic phosphorus according to Bell and Doisy¹⁴⁷. Inorganic sulphates according to Denis¹⁵⁶. Protein was determined refractometrically.

V. TREATMENT.

It is not the intention to discuss the various methods of treatment employed throughout the world since this condition was recognized as a clinical entity. The purpose of this chapter is to emphasize briefly the treatment as it has been carried out the last three years in this school a regime which has been built up by Marriott, and which has shown very satisfactory results.

When we review the commonly used text books in pediatrics

we find that the main idea in the treatment of this condition is a longer or shorter starvation period, followed by small and then increasing doses of breast milk. The common doses are usually 5 gm. breast milk 5 times daily and then slowly or more rapidly increasing this amount, until the minimum caloric requirement calculated on the basis of the weight of the athreptic infant has been reached. If breast milk is not available the most common feeding has been Finkelstein and Meyer's¹⁵⁷ protein milk. The majority of pediatricians have taken the attitude that loose stools, often present in these cases, have to be stopped before the poor nutrition of the infant can be treated. The best way to stop a diarrhea was thought to be by reducing the total caloric intake, at the same time as the fermentation processes in the intestinal tract were reduced, by decreasing the sugar, and increasing the protein in the feeding. Protein milk fulfills both requirements. As it was originally made it corresponded to 370 calories per 1,000 cc. of milk. When the condition of the stools had improved the sugar content might be increased.

The pediatric school of Washington University has taken a wholly different point of view, as Marriott¹⁵⁸ has stated in his paper on artificial feeding of athreptic infants. The nutritional condition of the infant has been taken as the basis of the treatment. Attention has been centered on the food requirement of the organism. The character of the stools has been considered of secondary importance. If the nutritional condition of the infant has improved, even though the stools have a tendency to be loose, no change has been made in the feeding. This procedure has been followed without observing any harmful effect on the infant's condition. Believing that partial starvation is one of the causes of the condition, rather than a means of preventing it, it is felt that conditions in the intestinal tract will clear up more rapidly if the body cells, including those of the intestinal tract, are provided with sufficient amounts of food. That diarrhea may result from underfeeding has long been realized in this school. In other words, it has been well recognized that a starvation diarrhea exists and is not infrequent.

Talbot¹⁴² has recently made some metabolism studies on the heat output of athreptic infants, and has shown that the metabolism calculated on the basis of actual weight falls outside

the 10 per cent. average normal limits, when infants are 20 per cent. or more below the average weight, and that the more the infant is under weight the greater the heat output per kilo of body weight. It is conceivable then that the food requirement of these infants is considerably higher than those of normal infants of the same age. In fact, the requirement should be calculated rather on the basis of the expected weight for the age than on the actual observed weight. On account of the increased heat loss in these infants it is evident that the earlier limited doses of food calculated to 70 to 100 calories per kilo are too small. Such a feeding is partial starvation for these patients, and a caloric intake of from 150 to 200 per kilo of body weight is very often needed before a gain in weight occurs.

Some of the German pediatricians seem to have recently come to similar conclusions. The danger of carbohydrate deprivation is now emphasized. In the text book of Finkelstein, 1921, considerable attention is given to starvation and starvation diarrhea. In a recent article R. Lederer¹⁵⁹ describes the various symptoms of underfeeding on the breast, and mentions that both vomiting and diarrheal stools are common, which symptoms disappear when sufficient amounts of food are given. Lust¹⁶⁰ mentioned at the Jena Congress in May 1921 that he had seen the most extreme degree of atrophy develop at the breast, and emphasized the necessity of supplementary feeding of such infants. Most of those discussing his paper agreed with him.

Pediatricians all over the world seem entirely independently of each other to have realized the danger which underfeeding carries with it, especially in these undernourished infants.

As to the kind of feeding, Langstein in his recently published text book emphasizes rather strongly that in athrepsia no food other than breast milk must be given, because, as he says, there is no other feeding which gives these infants the same immunity. He starts with 40 calories per kilo of body weight, and increases daily with 30 and 40 gm. until the minimum caloric requirement is reached. The breast milk feeding is continued for at least three months.

Besides breast milk, Marriott's whole lactic acid milk mixture has been used in this clinic during the last four years with

excellent results. In some cases the milk given has been diluted with water, in other cases the milk has been given undiluted. The undiluted artificially-soured whole milk is enriched by the addition of commercial corn syrup, which latter is a mixture of dextrin, maltose and dextrose. From 45 to 75 cubic centimeters of the syrup, equivalent to the same number of grams of carbohydrate, are added to the day's feeding. This is a concentrated food of high caloric value, (750 to 1,000 calories per 1,000 Cc.).

The fear of high carbohydrate feeding which has previously existed seems to be unfounded. These infants seem to be able to use the carbohydrate very well, and as has been shown above the absorption of carbohydrate from the intestinal tract is very good. Mattil, Meyer and Grulee¹⁶¹ have furthermore found that the glucose tolerance in athreptic infants is higher than in normal infants. For normal infants the tolerance was found to be 0.8 to 0.9 gm. per kilo of body weight per hour, while in no case of athrepsia was the tolerance below 1.4 or 1.5 gm. per kilo per hour. The tolerance, that is, the appearance of sugar in the urine after intravenous injection, depends on the amount of sugar injected in the unit of time independent of the concentration of the sugar solution. Fleming¹³⁵ found that the tolerance for glucose, when given by mouth, was 3 gm. per kilo of body weight, and could go up to 6.6 gm. per kilo of body weight. In athrepsia there is furthermore a hypoglycemia present. While the normal infant's blood sugar taken 3-4 hours after the last feeding ranges from 0.06 to 0.09 per cent. with an average of 0.068 per cent. (Guy¹⁶²) and 0.07 to 0.14 (Coblner¹⁶³). The figures for athreptic infants are for 9 cases 0.04 to 0.07 with increase when nutrition is improved (Coblner¹⁶³). One case 0.046 (Chapin and Myers¹⁶⁴). The blood sugar seemed to be especially low in cases of athrepsia with vomiting (Guy¹⁶²). The high glucose tolerance and the hypoglycemia may be referred back to the same cause, probably a depletion of the glycogen store and the rapid combustion of carbohydrate. These findings indicate the great carbohydrate need of these infants.

Other steps in the treatment of athrepsia are based on the same principle, namely providing the sufficient number of calories. Intravenous injections of 10 per cent. glucose and 5 per cent. glucose plus 10 per cent. acacia or injection of whole

blood have been used rather extensively, in this clinic. In a critical moment when the vitality of the infant is low, and especially when vomiting, has been prominent, such intravenous injections are of distinct advantage. During the last three years 102 athreptic infants have been seen and injections have been done in 67 cases without noticeable effect. The longitudinal sinus has usually been used for the intravenous injections. If it has been possible to get blood from the parents or someone in the hospital a transfusion has been performed (citrate method; 50 to 100 cc. of blood being injected). Besides these intravenous glucose injections and transfusions the intraperitoneal saline has been administered in the same number of cases. The intraperitoneal saline injection is preferable to the subcutaneous administration. More fluid can be given to the organism in this way without subjecting the patient to discomfort. Sometimes a more or less marked degree of distention has been noted which has rapidly disappeared, otherwise no harmful effect has been seen.

Stimulants have in general proven of very little value. Camphorated oil and caffeine have been used during the stage of collapse but it seems doubtful if life has been saved by these means.

As this system of treatment has been more and more closely followed, the mortality figures of the athreptic infants treated in the hospital have decreased from 78 per cent. 1919, to 51 per cent. 1920, to 30 per cent., 1921 and 33 per cent. of the infants seen up to August 1922.

Figure 11 will show a curve of one of these infants, in which several injections were necessary in the beginning, and where the feeding was breast milk, later whole lactic acid milk.

One three weeks old baby, admitted in a miserable condition, weighing 2,560 gm., complaint was failure to gain weight. Mother sick in the hospital. Family history otherwise unknown. Past history: a full term normal baby, birth weight unknown. No snuffles, no eruptions or convulsions. Has never been given breast milk, has been fed on whole milk formula, whole milk 360cc., water 360cc., sugar 30 gm. 8x90cc. Infant does not take feeding well. Bowels: 1 or 2 yellow movements daily, stools never watery. Weight has been stationary since birth. Physical examination: Patient is a very small, poorly nourished infant of 3 weeks. Feature pinched, eyes sunken, color gray, skin over body very loose and dry. Abdomen large and flat. There is no evidence of acidosis. Extremities are very wasted. Mucous membranes have a good color. The physical examination otherwise negative. Note of

admitting officer later on day of admission when infant had been observed is as follows: Baby very small, and wasted, has been fed on good formula but failed to gain. Vomits some, will not take feeding well. Stools numerous, of starvation type. Examination negative except for poor nutrition. Child has done poorly simply because of poor nursing care. Will not take feeding well, and has not been forced sufficiently. Athrepsia and starvation stools show patient has had less than sustenance diet. Put on whole lactic acid milk formula. Von Pirquet reaction and Wassermann reaction negative. Urine negative. After 14 days in the hospital the infant, as is seen from the curve, started to gain weight, and 2 months later was discharged in a good condition.

VI. SUMMARY.

I. *Nomenclature*. — An etiological classification of the chronic nutritional disturbances has been unsatisfactory for the following reasons: the cases seen rarely fall into the groups mentioned. In the majority of the cases the causative factor is not a single one. In most cases both the alimentary and infectious factor are present. The clinical picture of the infant is furthermore not indicative of the preceeding causative factor. The treatment is usually based on the clinical findings irrespective of what the causes might have been. A clinical classification of the nutritional disorders seems to be the only one justifiable at present.

II. *Etiology*. — On the basis of the cases studied it is believed that faulty feeding is the main factor in the etiology of athrepsia, and that a quantitative and especially a qualitative starvation is responsible for the development of most cases. A constitutional inferiority does not seem to have played any important rôle in the development of the picture. The family histories of the patients have in most cases been entirely negative. The infants who have been followed, subsequent to discharge from the hospital, have developed into normal individuals. In addition, it is believed that parenteral infection is an important contributing factor in lowering the vitality of artificially fed infants, and renders them less able to thrive on artificial feeding. A stagnation of the stomach and upper intestinal content takes place. A coli invasion follows, and the nutritional disturbance is initiated.

III. *Symptomatology*. — In athreptic infants there is usually present an absolute and also a relative anemia. All these infants have shown some enlargement of the inguinal glands but

no general glandular enlargement has been observed. No duodenal ulcers have been found at autopsy. Acute gastro-intestinal disturbances, with diarrhea and vomiting, are very common. They occurred in 63 per cent. of the cases.

IV. *Pathogenesis.* — The pathogenesis of athrepsia has been considered as a negative energy balance, due to insufficient absorption of food from the gastro-intestinal tract (Heubner). A process of demineralization is considered an important factor by Czerny and by Finkelstein. The decrease in blood volume and volume flow of the blood is believed by Marriott to be an important factor in maintaining the condition once it has developed.

The blood protein is found to range about 4-5 per cent. considerably below that of normal infants, which show values from 6-6½ per cent. throughout the first year of life. This low protein in athreptic infant's blood serum may partly be due to the preceeding feeding low in protein and high in carbohydrates; partly to the lack of power on the part of the organism to build up protein.

The athreptic infants show a very low rate of blood flow which is in some instances due partly to the diminished blood volume, in other instances to constriction of the peripheral small vessels, in order to accomplish the distribution of the blood to the internal organs. The low blood flow is not usually accompanied by lowering of blood pressure.

This low rate of blood flow will contribute in lessening the resistance of these infants by depriving the body tissues of the necessary food with insufficient removal of water products and in this way contribute to the break-down of the body cells.

Experiments on rabbits have shown that during complete starvation with deprivation of fluid, the blood volume falls below the normal value for the body surface, as the result of water loss from the blood. However, by giving only enough food and water to prevent further weight loss, the blood volume is usually rapidly restored and quickly reaches a value above normal for the body surface. Those animals in whom the normal blood volume was not regained did not do well, and would not gain in weight, even if food was given in abundant amount. It is only fair to attribute the poor condition of these four young animals, in part, to the low blood volume. When we apply these findings to infants we can see that in

athreptic infants who show a lowering of blood volume, all the above mentioned factors will still further effect the organism, and all factors will work together in lowering the oxidizing power of the body cells and favor a breaking down of body tissue.

In the case of infants suffering from athrepsia, there is a diminished capacity of the organism to bring about such oxidations as the transformation of benzol to phenol.

In the urine of athreptic infants the caloric-nitrogen and carbon-nitrogen ratios are high, as compared with normal infants. This is an indication of excretion of an excessive amount of organic material, containing little or no nitrogen. There is no increase in the urinary excretion of creatinin, uric acid, or amino-acid nitrogen in the urine of athreptic infants. During the severe stages of athrepsia there is an increased excretion of organic acids in the urine (as determined by titration). The ammonia excretion in the urine of athreptic infants is, in a general way, proportionate to the amount of organic acids present, and with the improvement in the nutritional condition the excretion of organic acids and of ammonia decreases. These organic acids are for the greater part insoluble in ether and behave in a manner similar to the oxy-proteic acids.

There is a greatly increased loss of food material in the stools during the severe stages of athrepsia. This loss as determined by the bomb calorimeter may be as great as 26 per cent. of the food intake. With improvement in the nutritional condition of the infant, the utilization of food is much greater. This high caloric loss seems mostly to be due to a low absorption for fat. Absorption for nitrogen and carbohydrates is nearly normal.

Nitrogen retention is either negative or lower than normal in most cases. This negative or low nitrogen retention is accompanied by a loss of sodium chloride and calcium.

Of the blood salts, sodium is lower than normal merely as a result of the low protein in these cases. Inorganic phosphorus of the serum is low. This fact, in connection with the impaired calcium metabolism, may be considered an expression of abnormal osseous metabolism.

The main features in the pathogenesis of athrepsia considered in this study, develop naturally one from the other. The

diminished flow of the blood lowers the metabolism with excretion of unmetabolized constituents in the urine, resulting in a deficient utilization of food, particularly of nitrogen, with secondary disturbances in salt metabolism.

V. *Treatment*.—The relatively high heat output indicates that these infants have a high caloric need. The 70-100 calories per kilo of body weight sufficient to give gain in weight in a normal infant are not sufficient for an athreptic infant. If the caloric loss is covered, nothing will be left for growth, and the undernourished condition will continue. The sugar tolerance of these infants is higher than that of normal infants. The feeding, therefore, should be of high caloric value. This is accomplished by adding easily digested carbohydrate to a whole lactic acid milk feeding. In any emergency due to the poor nutrition a glucose injection or a transfusion has proved of great value. The circulation is improved and food is in this way given to the organism, without passage through the intestinal tract, already low in absorptive power.

It gives me great pleasure to extend my sincere thanks to Professor W. McKim Marriott from whom the ideas of this study originated and by whose encouraging help and invaluable assistance it has been possible to carry out this work. To his views also I am indebted for the principles expressed in describing the condition considered in this paper. In addition it has been a great privilege to be able to use the complete notes on cases from the records of the St. Louis Children's Hospital and the abundant facilities of the laboratories.

I wish also to express my gratitude to Dr. S. W. Clausen for the advice and valuable criticism he has given in the chemical conduct of the work.

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